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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Magali Bourghol	Hickey	Medford, MA

Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

MODAFINIL COMPOSITIONS

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ Customer Number:

OR

☑ Firm or Individual Name	Transform Pharmaceuticals, Inc.				
Address	29 Hartwell Avenue				781-674-7852
Address					
City	Lexington	State	MA	Zip	02421
Country	USA	Telephone		Fax	

ENCLOSED APPLICATION PARTS ***(check all that apply)***

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Respectfully submitted,

SIGNATURE John Lucas

TYPED or PRINTED NAME JOHN LUCAS

TELEPHONE 781 674 7852

Date February 6, 2004

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Docket Number TPIP044A+

INVENTOR(S)/APPLICANT(S)

Given Name (first and middle [if any])	Family or Surname	Residence (City and either State or Foreign Country)
Matthew	Peterson	Framingham, MA
Orn	Almarsson	Shrewsbury, MA
Mark	Oliveira	Newton, MA

Number _____ of _____

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Attorney Docket No. TPIP044A+

MODAFINIL COMPOSITIONS

Inventors:

Magali Bourghol Hickey
Medford, MA

Matthew Peterson
Framingham, MA

Orn Almarsson
Shrewsbury, MA

Mark Oliveira
Newton, MA

MODAFINIL COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to API-containing compositions, pharmaceutical compositions comprising such APIs, and methods for preparing same.

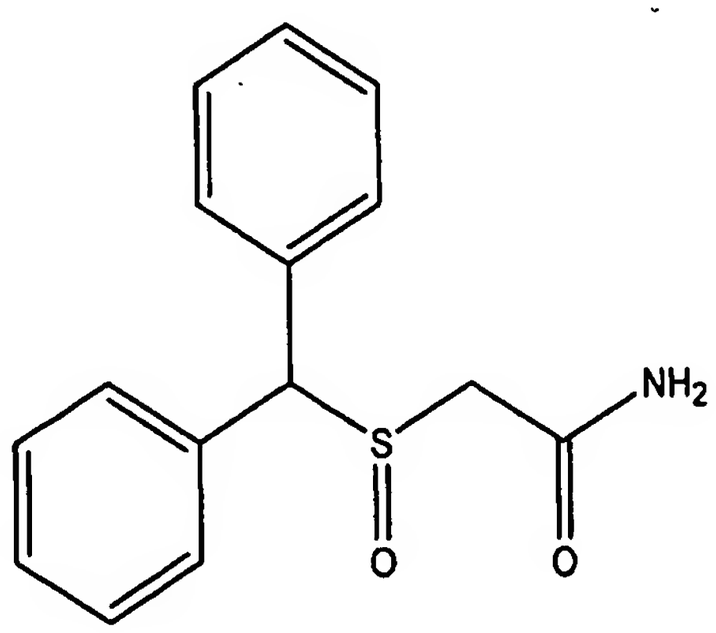
BACKGROUND OF THE INVENTION

Active pharmaceutical ingredients (API or APIs (plural)) in pharmaceutical compositions can be prepared in a variety of different forms. Such APIs can be prepared so as to have a variety of different chemical forms including chemical derivatives or salts. Such APIs can also be prepared to have different physical forms. For example, the APIs may be amorphous, may have different crystalline polymorphs, or may exist in different solvation or hydration states. By varying the form of an API, it is possible to vary the physical properties thereof. For example, crystalline polymorphs typically have different solubilities from one another, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapour pressure, density, colour, and compressibility. Accordingly, variation of the crystalline state of an API is one of many ways in which to modulate the physical properties thereof.

It would be advantageous to have new forms of these APIs that have improved properties, in particular, as oral formulations. Specifically, it is desirable to identify improved forms of APIs that exhibit significantly improved properties including increased aqueous solubility and stability. Further, it is desirable to improve the processability, or preparation of pharmaceutical formulations. For example, needle-like crystal forms or habits of APIs can cause aggregation, even in compositions where the API is mixed with other substances, such that a non-uniform mixture is obtained. It is also desirable to increase the dissolution rate of API-containing pharmaceutical compositions in water, increase the bioavailability of orally-administered compositions, and provide a more rapid onset to therapeutic effect. It is also desirable to have a form of

the API which, when administered to a subject, reaches a peak plasma level faster, has a longer lasting therapeutic plasma concentration, and higher overall exposure when compared to equivalent amounts of the API in its presently-known form.

Modafinil, an API used to treat subjects with narcolepsy, is practically insoluble in water. Modafinil(CAS Registry Number: 68693-11-8) is represented by the structure (I):



(I)

It would be advantageous to have new forms of modafinil that have improved properties, in particular, as oral formulations. Specifically, it is desirable to identify improved forms of modafinil that exhibit significantly increased aqueous solubilities and both chemical and form stability. It is also desirable to increase the dissolution rate of API-containing pharmaceutical compositions in water, increase the bioavailability of orally-administered compositions, and provide a more rapid onset to therapeutic effect. It is also desirable to have a form of the API which, when administered to a subject, reaches a peak plasma level faster and/or has a longer lasting plasma concentration and higher overall exposure at high doses when compared to equivalent amounts of the API in its presently-known form.

SUMMARY OF THE INVENTION

It has now been found that co-crystals and solvates of modafinil can be obtained which have different properties as compared to the free form of the API.

Accordingly, in a first aspect, the present invention provides a co-crystal of modafinil, wherein the co-crystal former is an ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, or pyridine.

The invention further provides a pharmaceutical composition comprising a co-crystal of modafinil. Typically, the pharmaceutical composition further comprises one or more pharmaceutically-acceptable carriers, diluents or excipients. Pharmaceutical compositions according to the invention are described in further detail below.

In a further aspect, the present invention provides a process for the preparation of a co-crystal of modafinil, which comprises:

(1) providing modafinil;

(2) providing a co-crystal former which has at least one functional group selected from the group consisting of ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, or pyridine;

(3) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with the co-crystal former under crystallization conditions, so as to form a solid phase; and

(4) isolating co-crystals comprising modafinil and the co-crystal former.

In a further aspect, the present invention provides a process for modulating the solubility of modafinil for use in a pharmaceutical composition, which process comprises:

(1) providing modafinil;

(2) providing a co-crystal former which has at least one functional group selected from the group consisting of ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, or pyridine;

(3) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with the co-crystal former under crystallization conditions, so as to form a solid phase; and

(4) isolating co-crystals comprising modafinil and the co-crystal former.

In a further aspect, the present invention provides a process for modulating the dissolution of modafinil, whereby the aqueous dissolution rate or the dissolution rate in simulated gastric fluid or in simulated intestinal fluid, or in a solvent or plurality of solvents is increased, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with a co-crystal former under crystallization conditions, so as to form a co-crystal of modafinil and the co-crystal former; and

(2) isolating co-crystals comprising modafinil and the co-crystal former.

In one embodiment, the dissolution of modafinil is increased.

In a further aspect, the present invention provides a process for modulating the bioavailability of modafinil, whereby the AUC is increased, the time to T_{max} is reduced,

the length of time the concentration of modafinil is above ½ T_{max} is increased, or C_{max} is increased, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with a co-crystal former under crystallization conditions, so as to form a co-crystal of modafinil and the co-crystal former; and

(2) isolating co-crystals comprising modafinil and the co-crystal former.

In a further aspect, the present invention provides a process for modulating the dose response of modafinil for use in a pharmaceutical composition, which process comprises:

(1) providing modafinil;

(2) providing a co-crystal former which has at least one functional group selected from the group consisting of ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, or pyridine;

(3) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with the co-crystal former under crystallization conditions, so as to form a solid phase; and

(4) isolating co-crystals comprising modafinil and the co-crystal former.

In a still further aspect the present invention provides a process for improving the stability of modafinil (as compared to a reference form such as its free form), which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with a co-crystal former under crystallization conditions, so as to form a co-crystal of modafinil and the co-crystal former; and

(2) isolating co-crystals comprising modafinil and the co-crystal former.

In a still further aspect the present invention provides a process for modifying the morphology of modafinil, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with a co-crystal former under crystallization conditions, so as to form a co-crystal of the modafinil and the co-crystal former; and

(2) isolating co-crystals comprising the modafinil and the co-crystal former.

In a still further aspect, the present invention therefore provides a process of screening for co-crystal compounds, which comprises:

(1) providing (*i*) modafinil and (*ii*) a co-crystal former; and

(2) screening for co-crystals of modafinil with a co-crystal former by subjecting each combination of modafinil and co-crystal former to a procedure comprising:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with the co-crystal former under crystallization conditions so as to form a solid phase; and

(b) isolating co-crystals comprising modafinil and the co-crystal former.

An alternative embodiment is drawn to a process of screening for co-crystal compounds, which comprises:

(1) providing (*i*) modafinil and (*ii*) a plurality of different co-crystal formers; and

(2) screening for co-crystals of modafinil with co-crystal formers by subjecting each combination of modafinil and co-crystal former to a procedure comprising:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with the co-crystal former under crystallization conditions so as to form a solid phase; and

(b) isolating co-crystals comprising modafinil and the co-crystal former.

In a further aspect, the present invention provides a co-crystal composition comprising a co-crystal, wherein said co-crystal comprises modafinil and a co-crystal former. In further embodiments the co-crystal has an improved property as compared to the free form (which includes hydrates and solvates). In further embodiments, the improved property is selected from the group consisting of: increased solubility, increased dissolution, increased bioavailability, increased dose response, or other property described herein.

The processes according to the present invention may each comprise a further step or steps in which the modafinil co-crystal produced thereby is incorporated into a pharmaceutical composition.

In a still further aspect of the invention, a method is provided for treating a subject, preferably a human subject, suffering from excessive daytime sleepiness associated with narcolepsy where modafinil is an effective active pharmaceutical for said disorder. The method comprises administering to the subject a therapeutically-effective amount of a co-crystal or a solvate comprising modafinil.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1- PXRD diffractogram of a co-crystal comprising modafinil and malonic acid (Form I).

Figure 2- DSC thermogram of a co-crystal comprising modafinil and malonic acid.

Figure 3- TGA thermogram of a co-crystal comprising modafinil and malonic acid.

Figure 4A and 4B- Raman spectrum of a co-crystal comprising modafinil and malonic acid (Figure 4A), and three Raman spectra of modafinil (bottom spectrum), malonic acid (middle spectrum), and a co-crystal comprising modafinil and malonic acid (top spectrum) (Figure 4B).

Figure 5A and 5B- Infrared spectrum of a co-crystal comprising modafinil and malonic acid (Figure 5A), and three Infrared spectra of modafinil (top spectrum), malonic acid (middle spectrum), and a co-crystal comprising modafinil and malonic acid (bottom spectrum) (Figure 5B).

Figure 6- PXRD diffractogram of a co-crystal comprising modafinil and malonic acid (Form I).

Figure 7- Packing diagram for modafinil:malonic acid co-crystal (Form I).

Figure 8- PXRD diffractogram of a co-crystal comprising modafinil and malonic acid (Form II).

Figures 9A and 9B- PXRD diffractograms of a co-crystal comprising modafinil and glycolic acid, background removed and as collected, respectively.

Figures 10A and 10B- PXRD diffractograms of a co-crystal comprising modafinil and maleic acid, background removed and as collected, respectively.

Figure 11- PXRD diffractogram of a co-crystal comprising modafinil and L-tartaric acid.

Figure 12- PXRD diffractogram of a co-crystal comprising modafinil and citric acid.

Figures 13A and 13B- PXRD diffractogram of a co-crystal comprising modafinil and succinic acid, background removed and as collected, respectively .

Figure 14- DSC thermogram of a co-crystal comprising modafinil and succinic acid.

Figure 15- PXRD diffractogram of a co-crystal comprising R-(-)-modafinil and malonic acid.

Figure 16- DSC thermogram of a co-crystal comprising R-(-)-modafinil and malonic acid.

Figure 17- PXRD diffractogram of a co-crystal comprising R-(-)-modafinil and succinic acid.

Figure 18- DSC thermogram of a co-crystal comprising R-(-)-modafinil and succinic acid.

Figure 19- PXRD diffractogram of a co-crystal comprising R-(-)-modafinil and citric acid.

Figure 20- DSC thermogram of a co-crystal comprising R-(-)-modafinil and citric acid.

Figure 21- PXRD diffractogram of a solvate comprising modafinil and acetic acid.

Figure 22- TGA thermogram of a solvate comprising modafinil and acetic acid.

Figure 23- DSC thermogram of a solvate comprising modafinil and acetic acid.

Figure 24- Raman spectrum of a solvate comprising modafinil and acetic acid.

Figure 25- PXRD diffractogram of a solvate comprising modafinil and tetrahydrofuran.

Figure 26- PXRD diffractogram of a solvate comprising modafinil and 1,4-dioxane.

Figure 27- PXRD diffractogram of a solvate comprising modafinil and methanol.

Figure 28- TGA thermogram of a solvate comprising modafinil and methanol.

Figure 29- DSC thermogram of a solvate comprising modafinil and methanol.

Figure 30- PXRD diffractogram of a solvate comprising modafinil and nitromethane.

Figure 31- PXRD diffractogram of a possible solvate comprising modafinil and acetone.

Figure 32- PXRD diffractogram of a possible solvate comprising modafinil and 1,2-dichloroethane.

Figure 33- PXRD diffractogram of a polymorph of modafinil (Form VII).

Figure 34- Dissolution profile of several formulations of modafinil free form and modafinil:malonic acid (Form I).

Figure 35- PXRD diffractogram of a polymorph of R-(-)-modafinil (Form I).

Figure 36- PXRD diffractogram of a polymorph of R-(-)-modafinil (Form II).

Figure 37- PXRD diffractogram of a polymorph of R-(-)-modafinil (Form III).

Figure 38- PXRD diffractogram of a polymorph of R-(-)-modafinil (Form IV).

DETAILED DESCRIPTION OF THE INVENTION

The term "co-crystal" as used herein means a crystalline material comprised of two or more unique solids at room temperature, each containing distinctive physical characteristics, such as structure, melting point, and heats of fusion, with the exception that, if specifically stated, the API may be a liquid at room temperature. The co-crystals of the present invention comprise a co-crystal former H-bonded to modafinil or a derivative thereof. The co-crystal former may be H-bonded directly to modafinil or may be H-bonded to an additional molecule which is bound to modafinil. The additional molecule may be H-bonded to modafinil or bound ionically or covalently to modafinil. The additional molecule could also be a different API. Solvates of modafinil compounds that do not further comprise a co-crystal former are not co-crystals according to the

present invention. The co-crystals may however, include one or more solvate molecules in the crystalline lattice. That is, solvates of co-crystals, or a co-crystal further comprising a solvent or compound that is a liquid at room temperature, is included in the present invention, but crystalline material comprised of only modafinil and one or more liquids (at room temperature) are not included in the present invention. Other modes of molecular recognition may also be present including, pi-stacking, guest-host complexation and van der Waals interactions. Of the interactions listed above, hydrogen-bonding is the dominant interaction in the formation of the co-crystal, (and a required interaction according to the present invention) whereby a non-covalent bond is formed between a hydrogen bond donor of one of the moieties and a hydrogen bond acceptor of the other. Hydrogen bonding can result in several different intermolecular configurations. For example, hydrogen bonds can result in the formation of dimers, linear chains, or cyclic structures. These configurations can further include extended (two-dimensional) hydrogen bond networks and isolated triads. An alternative embodiment provides for a co-crystal wherein the co-crystal former is a second API. In another embodiment, the co-crystal former is not an API. For purposes of the present invention, the chemical and physical properties of modafinil in the form of a co-crystal may be compared to a reference compound that is modafinil in a different form. The reference compound may be specified as a free form, or more specifically, an anhydrate or hydrate of a free form, or more specifically, for example, a hemihydrate, monohydrate, dihydrate, trihydrate, quadrahydrate, pentahydrate; or a solvate of a free form. For example, the reference compound for modafinil in free form co-crystallized with a co-crystal former can be modafinil in free form. The reference compound may also be specified as crystalline or amorphous. The reference compound may also be specified as the most stable polymorph of the specified form of the reference compound.

The ratio of modafinil to co-crystal former may be stoichiometric or non-stoichiometric according to the present invention. Non-limiting examples such as, 1:1, 1:1.5, 1.5:1, 1:2, and 2:1 ratios of modafinil:co-crystal former are acceptable. In addition, co-crystals with vacancies within the crystalline lattice are included in the present invention. For example, a co-crystal with less than or about 0.01. 0.1, 1, 2, 3, 4, 5, 6, 7, 8,

9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 percent vacancies within the crystalline lattice are included in the present invention. The vacancies can be due to missing modafinil molecules or missing co-crystal former molecules from the crystalline lattice, or both.

It has surprisingly been found that when modafinil and a selected co-crystal former are allowed to form co-crystals, the resulting co-crystals give rise to improved properties of modafinil, as compared to modafinil in the free form, particularly with respect to: solubility, dissolution, bioavailability, stability, Cmax, Tmax, processability, longer lasting therapeutic plasma concentration, etc. For example, a co-crystal form of modafinil is particularly advantageous due to the low solubility of modafinil in water. Additionally, the co-crystal properties conferred upon modafinil are also useful because the bioavailability of modafinil can be improved and the plasma concentration and/or serum concentration of modafinil can be improved. This is particularly advantageous for orally-administrable formulations. Moreover, the dose response of modafinil can be improved, for example by increasing the maximum attainable response and/or increasing the potency of modafinil by increasing the biological activity per dosing equivalent.

Accordingly, in a first aspect, the present invention provides a pharmaceutical composition comprising a co-crystal of modafinil and a co-crystal former, such that the modafinil and the co-crystal former are capable of co-crystallizing from a solution phase under crystallization conditions or from the solid-state, for example, through grinding or heating. In another aspect, the co-crystal former which has at least one functional group selected from the group consisting of ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine, or a functional group in a Table herein, such that the modafinil and co-crystal former are capable of co-crystallizing from a solution phase under crystallization conditions.

In another embodiment, the use of an excess (more than 1 molar equivalent for a 1:1 co-crystal) of a co-crystal former can be used to drive the formation of stoichiometric co-crystals. For example, co-crystals with stoichiometries of 1:1, 2:1, or 1:2 can be produced by adding co-crystal former in an amount that is 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 50, 75, 100 times or more than the stoichiometric amount for a given co-crystal. Such an excessive use of a co-crystal former to form a co-crystal can be employed in solution or when grinding modafinil and a co-crystal former to cause co-crystal formation.

In another embodiment of the present invention, a modafinil co-crystal further comprises a co-crystal former which is hydrogen bonded via a preferred interaction between two or more functional groups. For example, modafinil and malonic acid co-crystallize through the interaction of a carboxylic acid functional group of the co-crystal former with sulfoxide and amide functional groups of modafinil.

In another embodiment of the present invention, the co-crystal comprises modafinil wherein the modafinil forms a dimeric primary amide structure via hydrogen bonds with an R^2_2 (8) motif. In such a structure, the NH_2 moiety can also participate in a hydrogen bond with a donor or an acceptor moiety from, for example, a co-crystal former or an additional (third) molecule, and the C=O moiety can participate in a hydrogen bond with a donor moiety from the co-crystal former or the additional molecule. In a further embodiment, the dimeric primary amide structure further comprises one, two, three, or four hydrogen bond donors. In a further embodiment, the dimeric primary amide structure further comprises one or two hydrogen bond acceptors. In a further embodiment, the dimeric primary amide structure further comprises a combination of hydrogen bond donors and acceptors. For example, the dimeric primary amide structure can further comprise one hydrogen bond donor and one hydrogen bond acceptor, one hydrogen bond donor and two hydrogen bond acceptors, two hydrogen bond donors and one hydrogen bond acceptor, two hydrogen bond donors and two hydrogen bond acceptors, or three hydrogen bond donors and one hydrogen bond acceptor.

The co-crystals of the present invention are formed where modafinil and the co-crystal former are bonded together through hydrogen bonds. Other non-covalent interactions, including pi-stacking and van der Waals interactions, may also be present.

In one embodiment, the co-crystal former is selected from the co-crystal formers of Table I and Table II. In other embodiments, the co-crystal former of Table I is specified as a Class 1, Class 2, or Class 3 co-crystal former (see column labeled "class" Table I). Table I lists multiple pK_a values for co-crystal formers having multiple functionalities. It is readily apparent to one skilled in the art the particular functional group corresponding to a particular pK_a value.

In another embodiment the particular functional group of a co-crystal former interacting with modafinil is specified (see for example Table I, columns labeled "Functionality" and "Molecular Structure" and the column of Table II labeled "Co-Crystal Former Functional Group").

In another embodiment, the co-crystal comprises more than one co-crystal former. For example, two, three, four, five, or more co-crystal formers can be incorporated in a co-crystal with modafinil. Co-crystals which comprise two or more co-crystal formers and an API are bound together via hydrogen bonds. In one embodiment, incorporated co-crystal formers are hydrogen bonded to modafinil molecules. In another embodiment, co-crystal formers are hydrogen bonded to either the modafinil molecules or the incorporated co-crystal formers.

In each process according to the invention, there is a need to contact modafinil with the co-crystal former. This may involve grinding the two solids together or melting one or both components and allowing them to recrystallize. This may also involve either solubilizing modafinil and adding the co-crystal former, or solubilizing the co-crystal former and adding modafinil. Crystallization conditions are applied to modafinil and the co-crystal former. This may entail altering a property of the solution, such as pH or temperature and may require concentration of the solute, usually by removal of the solvent, typically by drying the solution. Solvent removal results in the concentration of both modafinil and the co-crystal former increasing over time so as to facilitate crystallization. For example, evaporation, cooling, or the addition of an antisolvent may be used to crystallize co-crystals. In another embodiment, a slurry comprising modafinil and a co-crystal former is used to form co-crystals. Once the solid phase comprising any crystals is formed, this may be tested as described herein.

The co-crystals obtained as a result of such process steps may be readily incorporated into a pharmaceutical composition by conventional means. Pharmaceutical compositions in general are discussed in further detail below and may further comprise a pharmaceutically-acceptable diluent, excipient or carrier.

In a further aspect, the present invention provides a process for the production of a pharmaceutical composition, which process comprises:

(1) providing modafinil;

(2) providing a co-crystal former which has at least one functional group selected from the group consisting of ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine or of Table I, II, or III;

(3) grinding, heating, co-subliming, co-melting, or contacting in solution the modafinil with the co-crystal former under crystallization conditions;

(4) isolating co-crystals formed thereby; and

(5) incorporating the co-crystals into a pharmaceutical composition.

In a still further aspect the present invention provides a process for the production of a pharmaceutical composition, which comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with a co-crystal former, under crystallization conditions, so as to form a solid phase;

(2) isolating co-crystals comprising the modafinil and the co-crystal former; and

(3) incorporating the co-crystals into a pharmaceutical composition.

Assaying the solid phase for the presence of co-crystals of modafinil and the co-crystal former may be carried out by conventional methods known in the art. For

example, it is convenient and routine to use powder X-ray diffraction techniques to assess the presence of co-crystals. This may be affected by comparing the diffractograms of modafinil, the crystal former and putative co-crystals in order to establish whether or not true co-crystals had been formed. Other techniques, used in an analogous fashion, include differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and Raman spectroscopy. Single crystal X-ray diffraction is especially useful in identifying co-crystal structures.

In a further aspect, the present invention therefore provides a process of screening for co-crystal compounds, which comprises:

(1) providing (*i*) modafinil and (*ii*) a co-crystal former; and

(2) screening for co-crystals of the modafinil with the co-crystal former by subjecting each combination of modafinil and co-crystal former to a procedure comprising:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the modafinil with the co-crystal former under crystallization conditions so as to form a solid phase; and

(b) isolating co-crystals comprising the modafinil and the co-crystal former.

An alternative embodiment is drawn to a process of screening for co-crystal compounds, which comprises:

(1) providing (*i*) modafinil and (*ii*) a plurality of different co-crystal formers; and

(2) screening for co-crystals of the modafinil with the co-crystal formers by subjecting each combination of the modafinil and the co-crystal formers to a procedure comprising:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the modafinil with each co-crystal former under crystallization conditions so as to form a solid phase; and

(b) isolating co-crystals comprising the modafinil and the co-crystal former.

Modafinil and some co-crystal formers of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, modafinil and several co-crystal formers of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention including, for example, *cis*- and *trans*-isomers, R- and S-enantiomers, and (D)- and (L)-isomers. Co-crystals of the present invention can include isomeric forms of either modafinil or the co-crystal former or both. Isomeric forms of modafinil and co-crystal formers include, but are not limited to, stereoisomers such as enantiomers and diastereomers. In one embodiment, a co-crystal can comprise racemic modafinil and/or a co-crystal former. In another embodiment, a co-crystal can comprise enantiomerically pure modafinil and/or a co-crystal former. In another embodiment, a co-crystal can comprise modafinil or a co-crystal former with an enantiomeric excess of about 50 percent, 55 percent, 60 percent, 65 percent, 70 percent, 75 percent, 80 percent, 85 percent, 90 percent, 95 percent, 96 percent, 97 percent, 98 percent, 99 percent, greater than 99 percent, or any intermediate value. Several non-limiting examples of stereoisomeric co-crystal formers include tartaric acid and malic acid.

Co-crystals comprising enantiomerically pure components (e.g., modafinil or co-crystal former) can give rise to chemical and/or physical properties which are modulated with respect to those of the corresponding co-crystal comprising a racemic component. For example, the modafinil:malonic acid co-crystal from Example 1 comprises racemic modafinil. Enantiomerically pure R-(-)-modafinil:malonic acid is included in the scope of the invention. Likewise, enantiomerically pure S-(+)-modafinil:malonic acid can is included in the scope of the invention. A co-crystal comprising an enantiomerically pure component can give rise to a modulation of, for example, activity, bioavailability, or solubility, with respect to the corresponding co-crystal comprising a racemic component. As an example, the co-crystal R-(-)-modafinil:malonic acid can have modulated properties as compared to the racemic modafinil:malonic acid co-crystal.

As used herein and unless otherwise specified, the term "racemic co-crystal" refers to a co-crystal which is comprised of an equimolar mixture of two enantiomers of

modafinil, the co-crystal former, or both. For example, a co-crystal comprising modafinil and a non-stereoisomeric co-crystal former is a "racemic co-crystal" only when there is present an equimolar mixture of the modafinil enantiomers. Similarly, a co-crystal comprising modafinil and a stereoisomeric co-crystal former is a "racemic co-crystal" only when there is present an equimolar mixture of the modafinil enantiomers and of the co-crystal former enantiomers.

As used herein and unless otherwise specified, the term "enantiomerically pure co-crystal" refers to a co-crystal which is comprised of modafinil and a stereoisomeric or non-stereoisomeric co-crystal former where the enantiomeric excess of the stereoisomeric species is greater than or equal to about 90 percent *ee* (enantiomeric excess).

In another embodiment, the present invention includes a pharmaceutical composition comprising a co-crystal with enantiomerically pure modafinil and/or co-crystal former wherein the bioavailability is modulated with respect to the racemic co-crystal. In another embodiment, the present invention includes a pharmaceutical composition comprising a co-crystal with enantiomerically pure modafinil and/or co-crystal former wherein the activity is modulated with respect to the racemic co-crystal. In another embodiment, the present invention includes a pharmaceutical composition comprising a co-crystal with enantiomerically pure modafinil and/or co-crystal former wherein the solubility is modulated with respect to the racemic co-crystal.

As used herein and unless otherwise specified, the term "enantiomerically pure" includes a composition which is substantially enantiomerically pure and includes, for example, a composition with greater than or equal to about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 percent enantiomeric excess.

As used herein, the term "modafinil" includes both the racemate and single enantiomers, but may be specifically set forth as the racemate, R-isomer, S-isomer, or any mixture of both R- and S-isomers.

In another embodiment, a pharmaceutical composition can be formulated to contain modafinil in co-crystal form as micronized or nano-sized particles. More specifically, another embodiment couples the processing of pure modafinil to a co-crystal form with the process of making a controlled particle size for manipulation into a pharmaceutical dosage form. This embodiment combines two processing steps into a

single step via techniques such as, but not limited to, grinding, alloying, or sintering (i.e., heating a powder mix). The coupling of these processes overcomes a serious limitation of having to isolate and store the bulk drug that is required for a formulation, which in some cases can be difficult to isolate (e.g., amorphous, chemically or physically unstable).

Solubility Modulation

In a further aspect, the present invention provides a process for modulating the solubility of modafinil, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with a co-crystal former under crystallization conditions, so as to form a co-crystal of modafinil and the co-crystal former; and

(2) isolating co-crystals comprising the modafinil and the co-crystal former.

In one embodiment, the solubility of modafinil is modulated such that the aqueous solubility is increased. Solubility of modafinil may be measured by any conventional means such as chromatography (e.g., HPLC) or spectroscopic determination of the amount of modafinil in a saturated solution, such as UV-spectroscopy, IR-spectroscopy, Raman spectroscopy, quantitative mass spectroscopy, or gas chromatography.

In another embodiment, the co-crystals, solvates, and polymorphs of the present invention can be compared with free form modafinil as found in PROVIGIL® (Cephalon, Inc.). (See US Reissued Patent No. RE37,516) For example, the bioavailability of an embodiment of the present invention can be compared with that of PROVIGIL. As embodiments of the present invention, solubility can be increased 2, 3, 4, 5, 7, 10, 15, 20, 25, 50, 75, or 100 times by making a co-crystal of the reference form (e.g., crystalline or amorphous free form, hydrate or solvate). Further aqueous solubility can be measured in simulated gastric fluid (SGF) or simulated intestinal fluid (SIF) rather than water. SGF (non-diluted) of the present invention is made by combining 1 g/L Triton X-100 and 2 g/L NaCl in water and adjusting the pH with 20 mM HCl to obtain a solution with a final pH=1.7 (SIF is 0.68% monobasic potassium phosphate, 1% pancreatin, and sodium hydroxide where the pH of the final solution is 7.5). The pH of

the solvent used may also be specified as 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, or 12, or any pH in between successive values.

Examples of embodiments includes: co-crystal compositions with an aqueous solubility, at 37 degrees C and a pH of 7.0, that is increased at least 5 fold over the reference form, co-crystal compositions with a solubility in SGF that is increased at least 5 fold over the reference form, co-crystal compositions with a solubility in SIF that is increased at least 5 fold over the reference form.

Dissolution Modulation

In another aspect of the present invention, the dissolution profile of modafinil is modulated whereby the aqueous dissolution rate or the dissolution rate in simulated gastric fluid or in simulated intestinal fluid, or in a solvent or plurality of solvents is increased. Dissolution rate is the rate at which API solids dissolve in a dissolution medium. For APIs whose absorption rates are faster than the dissolution rates (e.g., steroids), the rate-limiting step in the absorption process is often the dissolution rate. Because of a limited residence time at the absorption site, APIs that are not dissolved before they are removed from intestinal absorption site are considered useless. Therefore, the rate of dissolution has a major impact on the performance of APIs that are poorly soluble. Because of this factor, the dissolution rate of APIs in solid dosage forms is an important, routine, quality control parameter used in the API manufacturing process.

Dissolution rate = K S (C_s-C)

where K is dissolution rate constant, S is the surface area, C_s is the apparent solubility, and C is the concentration of API in the dissolution medium.

For rapid API absorption, C_s-C is approximately equal to C_s

The dissolution rate of modafinil may be measured by conventional means known in the art.

The increase in the dissolution rate of a co-crystal, as compared to the reference form (e.g., free form), may be specified, such as by 10, 20, 30, 40, 50, 60, 70, 80, 90, or

100%, or by 2, 3, 4, 5 ,6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 500, 1000, 10,000, or 100,000 fold greater than the reference form (e.g., free form) in the same solution. Conditions under which the dissolution rate is measured are the same as discussed above. The increase in dissolution may be further specified by the time the composition remains supersaturated before reaching equilibrium solubility.

Examples of above embodiments include: co-crystal compositions with a dissolution rate in aqueous solution, at 37 degrees C and a pH of 7.0, that is increased at least 5 fold over the reference form, co-crystal compositions with a dissolution rate in SGF that is increased at least 5 fold over the reference form, co-crystal compositions with a dissolution rate in SIF that is increased at least 5 fold over the reference form.

Bioavailability Modulation

The methods of the present invention are used to make a pharmaceutical modafinil formulation with greater solubility, dissolution, and bioavailability. Bioavailability can be improved via an increase in AUC, reduced time to T_{max}, (the time to reach peak blood serum levels), or increased C_{max}. The present invention can result in higher plasma concentrations of modafinil when compared to the free form (reference form).

AUC is the area under the plot of plasma concentration of API (not logarithm of the concentration) against time after API administration. The area is conveniently determined by the "trapezoidal rule": The data points are connected by straight line segments, perpendiculars are erected from the abscissa to each data point, and the sum of the areas of the triangles and trapezoids so constructed is computed. When the last measured concentration (C_n, at time t_n) is not zero, the AUC from t_n to infinite time is estimated by C_n/k_{el}.

The AUC is of particular use in estimating bioavailability of APIs, and in estimating total clearance of APIs (Cl_T). Following single intravenous doses, AUC = D/Cl_T, for single compartment systems obeying first-order elimination kinetics, where D is the dose; alternatively, AUC = C_0/k_{el}, where k_{el} is the API elimination rate constant.

With routes other than the intravenous, $AUC = F \cdot D/Cl_T$, where F is the absolute bioavailability of the API.

Thus, in a further aspect, the present invention provides a process for modulating the bioavailability of modafinil when administered in its normal and effective dose range as a co-crystal, whereby the AUC is increased or the time to T_{max} is increased, as compared to a reference form, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with a co-crystal former under crystallization conditions, so as to form a co-crystal of the modafinil and the co-crystal former; and

(2) isolating co-crystals comprising the modafinil and the co-crystal former.

Examples of the above embodiments include: co-crystal compositions with a time to T_{max} that is increased by at least 5% as compared to the reference form, co-crystal compositions with a time to T_{max} that is increased by at least 10% over the reference form, co-crystal compositions with a time to T_{max} that is increased by at least 15% over the reference form, co-crystal compositions with a time to T_{max} that is increased by at least 20% over the reference form, co-crystal compositions with a T_{max} that is increased by at least 25% over the reference form, co-crystal compositions with a T_{max} that is increased by at least 30% over the reference form, co-crystal compositions with a T_{max} that is increased by at least 35% over the reference form, co-crystal compositions with a T_{max} that is increased by at least 40% over the reference form, co-crystal compositions with an AUC that is increased by at least 5% over the reference form, co-crystal compositions with an AUC that is increased by at least 10% over the reference form, co-crystal compositions with an AUC that is increased by at least 15% over the reference form, co-crystal compositions with an AUC that is increased by at least 20% over the reference form, co-crystal compositions with an AUC that is increased by at least 25% over the reference form, co-crystal compositions with an AUC that is increased by at least 30% over the reference form, co-crystal compositions with an AUC that is increased by at least 35% over the reference form, co-crystal compositions with an AUC that is increased by at least 40% over the reference form. Other examples include wherein the reference form is crystalline, wherein the reference form is amorphous, or wherein the reference form is an anhydrous crystal of modafinil.

Dose Response Modulation

In a further aspect the present invention provides a process for improving the dose response of modafinil, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with a co-crystal former under crystallization conditions, so as to form a co-crystal of the modafinil and the co-crystal former; and

(2) isolating co-crystals comprising the modafinil and the co-crystal former.

Dose response is the quantitative relationship between the magnitude of response and the dose inducing the response and may be measured by conventional means known in the art. The curve relating effect (as the dependent variable) to dose (as the independent variable) for an API-cell system is the "dose-response curve". Typically, the dose-response curve is the measured response to an API plotted against the dose of the API (mg/kg) given. The dose response curve can also be a curve of AUC against the dose of the API given.

In an embodiment of the present invention, a co-crystal of the present invention has an increased dose response curve or a more linear dose response curve than the corresponding reference compound.

Increased Stability

In a still further aspect the present invention provides a process for improving the stability of modafinil (as compared to a reference form such as its free form), which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with a co-crystal former under crystallization conditions, so as to form a co-crystal of the modafinil and the co-crystal former; and

(2) isolating co-crystals comprising the modafinil and the co-crystal former.

In a preferred embodiment, the compositions of the present invention, including modafinil co-crystals, solvates, and formulations comprising modafinil, are suitably stable for pharmaceutical use. Preferably, modafinil or formulations thereof, of the present invention, are stable such that when stored at 30 degrees C for 2 years, less than 0.2 % of any one degradant is formed. The term degradant refers herein to product(s) of a single type of chemical reaction. For example, if a hydrolysis event occurs that cleaves a molecule into two products, for the purpose of the present invention, it would be considered a single degradant. More preferably, when stored at 40 degrees C for 2 years, less than 0.2 % of any one degradant is formed. Alternatively, when stored at 30 degrees C for 3 months, less than 0.2 % or 0.15 %, or 0.1 % of any one degradant is formed, or when stored at 40 degrees C for 3 months, less than 0.2 % or 0.15 %, or 0.1 % of any one degradant is formed. Further alternatively, when stored at 60 degrees C for 4 weeks, less than 0.2 % or 0.15 %, or 0.1 % of any one degradant is formed. The relative humidity (RH) may be specified as ambient RH, 75 % RH, or as any single integer between 1 to 99 % RH. In another embodiment, a single dose of the present invention comprises less than 0.5 %, 0.2 %, or 0.1 % degradants upon administration to a subject.

Morphology Modulation

In a still further aspect the present invention provides a process for modifying the morphology of modafinil, which process comprises:

(1) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with a co-crystal former under crystallization conditions, so as to form a co-crystal of the modafinil and the co-crystal former; and

(2) isolating co-crystals comprising the modafinil and the co-crystal former.

In an embodiment the co-crystal comprises or consists of modafinil and a co-crystal former wherein the interaction between the two, e.g., H-bonding, occurs between the amino group of modafinil and a co-crystal former with a corresponding interacting group of Table III. In a further embodiment, the co-crystal comprises modafinil and a co-crystal former of Table I or II. In an aspect of the invention, only co-crystals having an H-bond acceptor on the first molecule and an H-bond donor on the second molecule, where the first and second molecules are either co-crystal former and modafinil

respectively, or modafinil and co-crystal former respectively, are included in the present invention.

Pharmaceutically acceptable co-crystals can be administered by controlled- or delayed-release means. Controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled release counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include: 1) extended activity of the drug; 2) reduced dosage frequency; 3) increased patient compliance; 4) usage of less total drug; 5) reduction in local or systemic side effects; 6) minimization of drug accumulation; 7) reduction in blood level fluctuations; 8) improvement in efficacy of treatment; 9) reduction of potentiation or loss of drug activity; and 10) improvement in speed of control of diseases or conditions. Kim, Cherng-ju, Controlled Release Dosage Form Design, 2 (Technomic Publishing, Lancaster, Pa.: 2000).

Conventional dosage forms generally provide rapid or immediate drug release from the formulation. Depending on the pharmacology and pharmacokinetics of the drug, use of conventional dosage forms can lead to wide fluctuations in the concentrations of the drug in a patient's blood and other tissues. These fluctuations can impact a number of parameters, such as dose frequency, onset of action, duration of efficacy, maintenance of therapeutic blood levels, toxicity, side effects, and the like. Advantageously, controlled-release formulations can be used to control a drug's onset of action, duration of action, plasma levels within the therapeutic window, and peak blood levels. In particular, controlled- or extended-release dosage forms or formulations can be used to ensure that the maximum effectiveness of a drug is achieved while minimizing potential adverse effects and safety concerns, which can occur both from under dosing a drug (i.e., going below the minimum therapeutic levels) as well as exceeding the toxicity level for the drug.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of drug to maintain this level of

therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, ionic strength, osmotic pressure, temperature, enzymes, water, and other physiological conditions or compounds.

A variety of known controlled- or extended-release dosage forms, formulations, and devices can be adapted for use with the co-crystals and compositions of the invention. Examples include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,733,566; and 6,365,185 B1; each of which is incorporated herein by reference. These dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems (such as OROS® (Alza Corporation, Mountain View, Calif. USA)), multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Additionally, ion exchange materials can be used to prepare immobilized, adsorbed co-crystals and thus effect controlled delivery of the drug. Examples of specific anion exchangers include, but are not limited to, Duolite® A568 and Duolite® AP143 (Rohm & Haas, Spring House, PA. USA).

One embodiment of the invention encompasses a unit dosage form which comprises a pharmaceutically acceptable co-crystal, or a solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof, and one or more pharmaceutically acceptable excipients or diluents, wherein the pharmaceutical composition or dosage form is formulated for controlled-release. Specific dosage forms utilize an osmotic drug delivery system.

A particular and well-known osmotic drug delivery system is referred to as OROS® (Alza Corporation, Mountain View, Calif. USA). This technology can readily be adapted for the delivery of compounds and compositions of the invention. Various aspects of the technology are disclosed in U.S. Pat. Nos. 6,375,978 B1; 6,368,626 B1;

6,342,249 B1; 6,333,050 B2; 6,287,295 B1; 6,283,953 B1; 6,270,787 B1; 6,245,357 B1; and 6,132,420; each of which is incorporated herein by reference. Specific adaptations of OROS® that can be used to administer compounds and compositions of the invention include, but are not limited to, the OROS® Push-Pull™, Delayed Push-Pull™, Multi-Layer Push-Pull™, and Push-Stick™ Systems, all of which are well known. See, e.g., http://www.alza.com. Additional OROS® systems that can be used for the controlled oral delivery of compounds and compositions of the invention include OROS®-CT and L-OROS®. Id.; see also, Delivery Times, vol. II, issue II (Alza Corporation).

Conventional OROS® oral dosage forms are made by compressing a drug powder (e.g. co-crystal) into a hard tablet, coating the tablet with cellulose derivatives to form a semi-permeable membrane, and then drilling an orifice in the coating (e.g., with a laser). Kim, Cherng-ju, Controlled Release Dosage Form Design, 231-238 (Technomic Publishing, Lancaster, Pa.: 2000). The advantage of such dosage forms is that the delivery rate of the drug is not influenced by physiological or experimental conditions. Even a drug with a pH-dependent solubility can be delivered at a constant rate regardless of the pH of the delivery medium. But because these advantages are provided by a build-up of osmotic pressure within the dosage form after administration, conventional OROS® drug delivery systems cannot be used to effectively deliver drugs with low water solubility. Id. at 234. Because co-crystals of this invention can be far more soluble in water than modafinil itself, they are well suited for osmotic-based delivery to patients. This invention does, however, encompass the incorporation of conventional crystalline modafinil (e.g. pure modafinil without co-crystal former), and isomers and isomeric mixtures thereof, into OROS® dosage forms.

A specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a dry or substantially dry state drug layer located within the cavity adjacent to the exit orifice and in direct or indirect contacting relationship with the expandable layer; and a flow-promoting layer interposed between the inner surface of the wall and at least the external surface of the drug layer located within the cavity, wherein the drug layer comprises a co-

crystal, or a solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,368,626, the entirety of which is incorporated herein by reference.

Another specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a drug layer located within the cavity adjacent the exit orifice and in direct or indirect contacting relationship with the expandable layer; the drug layer comprising a liquid, active agent formulation absorbed in porous particles, the porous particles being adapted to resist compaction forces sufficient to form a compacted drug layer without significant exudation of the liquid, active agent formulation, the dosage form optionally having a placebo layer between the exit orifice and the drug layer, wherein the active agent formulation comprises a co-crystal, or a solvate, hydrate, dehydrate, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,342,249, the entirety of which is incorporated herein by reference.

Excipients employed in pharmaceutical compositions of the present invention can be solids, semi-solids, liquids or combinations thereof. Preferably, excipients are solids. Compositions of the invention containing excipients can be prepared by known technique of pharmacy that comprises admixing an excipient with an API or therapeutic agent. A pharmaceutical composition of the invention contains a desired amount of API per dose unit and, if intended for oral administration, can be in the form, for example, of a tablet, a caplet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a dispersion, a liquid, or any other form reasonably adapted for such administration. If intended for parenteral administration, it can be in the form, for example, of a suspension or transdermal patch. If intended for rectal administration, it can be in the form, for example, of a suppository. Presently preferred are oral dosage forms that are discrete dose units each containing a predetermined amount of the API, such as tablets or capsules.

Non-limiting examples follow of excipients that can be used to prepare pharmaceutical compositions of the invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable carriers or diluents as excipients. Suitable carriers or diluents illustratively include, but are not limited to, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (e.g., Celutab™ and Emdex™); mannitol; sorbitol; xylitol; dextrose (e.g., Cerelose™ 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; granular calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; celluloses including microcrystalline cellulose, food grade sources of alpha- and amorphous cellulose (e.g., RexcelJ), powdered cellulose, hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC); calcium carbonate; glycine; bentonite; block co-polymers; polyvinylpyrrolidone; and the like. Such carriers or diluents, if present, constitute in total about 5% to about 99%, preferably about 10% to about 85%, and more preferably about 20% to about 80%, of the total weight of the composition. The carrier, carriers, diluent, or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Lactose, mannitol, dibasic sodium phosphate, and microcrystalline cellulose (particularly Avicel PH microcrystalline cellulose such as Avicel PH 101), either individually or in combination, are preferred diluents. These diluents are chemically compatible with APIs. The use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a granulated composition) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides compositions having suitable release rates of APIs, stability, pre-compression flowability, and/or drying properties at a relatively low diluent cost. It provides a high density substrate that aids densification during granulation (where wet granulation is employed) and therefore improves blend flow properties and tablet properties.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable disintegrants as excipients, particularly for tablet formulations. Suitable disintegrants include, but are not limited to, either individually or

in combination, starches, including sodium starch glycolate (e.g., Explotab™ of PenWest) and pregelatinized corn starches (e.g., National™ 1551 of National Starch and Chemical Company, National™ 1550, and Colocorn™ 1500), clays (e.g., Veegum™ HV of R.T. Vanderbilt), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, croscarmellose sodium (e.g., Ac-Di-Sol™ of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

Disintegrants may be added at any suitable step during the preparation of the composition, particularly prior to granulation or during a lubrication step prior to compression. Such disintegrants, if present, constitute in total about 0.2% to about 30%, preferably about 0.2% to about 10%, and more preferably about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%, more preferably about 0.2% to about 7%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to granulated pharmaceutical compositions of the present invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powder being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Such binding agents may also prevent or inhibit crystallization or recrystallization of an API of the present invention once the salt has been dissolved in a solution. Suitable binding agents and adhesives include, but are not limited to, either individually or in combination, acacia; tragacanth; sucrose; gelatin; glucose; starches such as, but not limited to, pregelatinized starches (e.g., National™ 1511 and National™ 1500); celluloses such as, but not limited to, methylcellulose and carmellose sodium (e.g., Tylose™); alginic acid and salts of alginic acid; magnesium aluminum silicate; PEG; guar gum; polysaccharide acids; bentonites;

povidone, for example povidone K-15, K-30 and K-29/32; polymethacrylates; HPMC; hydroxypropylcellulose (e.g., Klucel™ of Aqualon); and ethylcellulose (e.g., Ethocel™ of the Dow Chemical Company). Such binding agents and/or adhesives, if present, constitute in total about 0.5% to about 25%, preferably about 0.75% to about 15%, and more preferably about 1% to about 10%, of the total weight of the pharmaceutical composition.

Many of the binding agents are polymers comprising amide, ester, ether, alcohol or ketone groups and, as such, are preferably included in pharmaceutical compositions of the present invention. Polyvinylpyrrolidones such as povidone K-30 are especially preferred. Polymeric binding agents can have varying molecular weight, degrees of crosslinking, and grades of polymer. Polymeric binding agents can also be copolymers, such as block co-polymers that contain mixtures of ethylene oxide and propylene oxide units. Variation in these units' ratios in a given polymer affects properties and performance. Examples of block co-polymers with varying compositions of block units are Poloxamer 188 and Poloxamer 237 (BASF Corporation).

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable wetting agents as excipients. Such wetting agents are preferably selected to maintain the API in close association with water, a condition that is believed to improve bioavailability of the composition.

Non-limiting examples of surfactants that can be used as wetting agents in pharmaceutical compositions of the invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (e.g., Labrasol™ of Gattefosse), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (e.g., Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol

laurate (e.g., Lauroglycol™ of Gattefosse), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the pharmaceutical composition.

Wetting agents that are anionic surfactants are preferred. Sodium lauryl sulfate is a particularly preferred wetting agent. Sodium lauryl sulfate, if present, constitutes about 0.25% to about 7%, more preferably about 0.4% to about 4%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants (including anti-adherents and/or glidants) as excipients. Suitable lubricants include, but are not limited to, either individually or in combination, glyceryl behapate (e.g., Compritol™ 888 of Gattefosse); stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils (e.g., Sterotex™ of Abitec); colloidal silica; talc; waxes; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; PEG (e.g., Carbowax™ 4000 and Carbowax™ 6000 of the Dow Chemical Company); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0. 1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the pharmaceutical composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet formulations.

Suitable anti-adherents include, but are not limited to, talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is a preferred anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1% to about 10%, more

preferably about 0.25% to about 5%, and still more preferably about 0.5% to about 2%, of the total weight of the pharmaceutical composition.

Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include, but are not limited to, colloidal silicon dioxide, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate. Colloidal silicon dioxide is particularly preferred.

Other excipients such as colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in pharmaceutical compositions of the present invention. Tablets can be coated, for example with an enteric coating, or uncoated. Compositions of the invention can further comprise, for example, buffering agents.

Optionally, one or more effervescent agents can be used as disintegrants and/or to enhance organoleptic properties of pharmaceutical compositions of the invention. When present in pharmaceutical compositions of the invention to promote dosage form disintegration, one or more effervescent agents are preferably present in a total amount of about 30% to about 75%, and preferably about 45% to about 70%, for example about 60%, by weight of the pharmaceutical composition.

According to a particularly preferred embodiment of the invention, an effervescent agent, present in a solid dosage form in an amount less than that effective to promote disintegration of the dosage form, provides improved dispersion of the API in an aqueous medium. Without being bound by theory, it is believed that the effervescent agent is effective to accelerate dispersion of the API, from the dosage form in the gastrointestinal tract, thereby further enhancing absorption and rapid onset of therapeutic effect. When present in a pharmaceutical composition of the invention to promote intragastrointestinal dispersion but not to enhance disintegration, an effervescent agent is preferably present in an amount of about 1% to about 20%, more preferably about 2.5% to about 15%, and still more preferably about 5% to about 10%, by weight of the pharmaceutical composition.

An "effervescent agent" herein is an agent comprising one or more compounds which, acting together or individually, evolve a gas on contact with water. The gas evolved is generally oxygen or, most commonly, carbon dioxide. Preferred effervescent agents comprise an acid and a base that react in the presence of water to generate carbon

dioxide gas. Preferably, the base comprises an alkali metal or alkaline earth metal carbonate or bicarbonate and the acid comprises an aliphatic carboxylic acid.

Non-limiting examples of suitable bases as components of effervescent agents useful in the invention include carbonate salts (e.g., calcium carbonate), bicarbonate salts (e.g., sodium bicarbonate), sesquicarbonate salts, and mixtures thereof. Calcium carbonate is a preferred base.

Non-limiting examples of suitable acids as components of effervescent agents and/or solid acids useful in the invention include citric acid, tartaric acid (as D-, L-, or D/L-tartaric acid), malic acid, maleic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides of such acids, acid salts of such acids, and mixtures thereof. Citric acid is a preferred acid.

In a preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the weight ratio of the acid to the base is about 1:100 to about 100:1, more preferably about 1:50 to about 50:1, and still more preferably about 1:10 to about 10:1. In a further preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the ratio of the acid to the base is approximately stoichiometric.

Excipients which solubilize metal salts of APIs typically have both hydrophilic and hydrophobic regions, or are preferably amphiphilic or have amphiphilic regions. One type of amphiphilic or partially-amphiphilic excipient comprises an amphiphilic polymer or is an amphiphilic polymer. A specific amphiphilic polymer is a polyalkylene glycol, which is commonly comprised of ethylene glycol and/or propylene glycol subunits. Such polyalkylene glycols can be esterified at their termini by a carboxylic acid, ester, acid anhyride or other suitable moiety. Examples of such excipients include poloxamers (symmetric block copolymers of ethylene glycol and propylene glycol; e.g., poloxamer 237), polyalkyene glycolated esters of tocopherol (including esters formed from a di- or multi-functional carboxylic acid; e.g., d-alpha-tocopherol polyethylene glycol-1000 succinate), and macrogolglycerides (formed by alcoholysis of an oil and esterification of a polyalkylene glycol to produce a mixture of mono-, di- and tri-glycerides and mono- and di-esters; e.g., stearoyl macrogol-32 glycerides). Such pharmaceutical compositions are advantageously administered orally.

Pharmaceutical compositions of the present invention can comprise about 10% to about 50%, about 25% to about 50%, about 30% to about 45%, or about 30% to about 35% by weight of API; about 10% to about 50%, about 25% to about 50%, about 30% to about 45%, or about 30% to about 35% by weight of a an excipient which inhibits crystallization; and about 5% to about 50%, about 10% to about 40%, about 15% to about 35%, or about 30% to about 35% by weight of a binding agent. In one example, the weight ratio of the API to the excipient which inhibits crystallization to binding agent is about 1 to 1 to 1.

Solid dosage forms of the invention can be prepared by any suitable process, not limited to processes described herein.

An illustrative process comprises (a) a step of blending a salt of the invention with one or more excipients to form a blend, and (b) a step of tableting or encapsulating the blend to form tablets or capsules, respectively.

In a preferred process, solid dosage forms are prepared by a process comprising (a) a step of blending an API salt of the invention with one or more excipients to form a blend, (b) a step of granulating the blend to form a granulate, and (c) a step of tableting or encapsulating the blend to form tablets or capsules respectively. Step (b) can be accomplished by any dry or wet granulation technique known in the art, but is preferably a dry granulation step. A salt of the present invention is advantageously granulated to form particles of about 1 micrometer to about 100 micrometer, about 5 micrometer to about 50 micrometer, or about 10 micrometer to about 25 micrometer. One or more diluents, one or more disintegrants and one or more binding agents are preferably added, for example in the blending step, a wetting agent can optionally be added, for example in the granulating step, and one or more disintegrants are preferably added after granulating but before tableting or encapsulating. A lubricant is preferably added before tableting. Blending and granulating can be performed independently under low or high shear. A process is preferably selected that forms a granulate that is uniform in API content, that readily disintegrates, that flows with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that is dense enough in bulk so that a batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet dies.

In an alternative embodiment, solid dosage forms are prepared by a process that includes a spray drying step, wherein the API is suspended with one or more excipients in one or more sprayable liquids, preferably a non-protic (e.g., non-aqueous or non-alcoholic) sprayable liquid, and then is rapidly spray dried over a current of warm air.

A granulate or spray dried powder resulting from any of the above illustrative processes can be compressed or molded to prepare tablets or encapsulated to prepare capsules. Conventional tableting and encapsulation techniques known in the art can be employed. Where coated tablets are desired, conventional coating techniques are suitable.

Excipients for tablet compositions of the invention are preferably selected to provide a disintegration time of less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or less, and still more preferably about 15 minutes or less, in a standard disintegration assay.

In another embodiment of the present invention, a pharmaceutical composition comprising modafinil and an additional API can be prepared. The modafinil and the additional API can be in the form of a co-crystal, or may be included as a mixture or a combination of active pharmaceutical ingredients. For example, a composition can comprise modafinil and caffeine as a combination. A composition comprising modafinil and caffeine can be used as a therapeutic agent to treat the same conditions as modafinil. In such a composition comprising modafinil and caffeine, the caffeine can yield a quick release characteristic to the dissolution profile while the modafinil causes the therapeutic effect to be present for hours after administration. Combination therapies comprise the administration of two or more APIs in the same formulation, or in two or more co-administered formulations. The APIs can be administered together at the same time, or individually at specified intervals.

Uses for modafinil are well known in the art and include the treatment of narcolepsy. The dosage and administration for modafinil compositions of the present invention can be determined using routine methods in the art but will generally fall between about 50 and about 700 mg/day.

EXAMPLES

General Methods for the Preparation of Co-Crystals

a) High Throughput crystallization using the CrystalMax™ platform

CrystalMax™ comprises a sequence of automated, integrated high throughput robotic stations capable of rapid generation, identification and characterization of polymorphs, salts, and co-crystals of APIs and API candidates. Worksheet generation and combinatorial mixture design is carried out using proprietary design software Architect™. Typically, an API or an API candidate is dispensed from an organic solvent into tubes and dried under a stream of nitrogen. Salts and/or co-crystal formers may also be dispensed and dried in the same fashion. Water and organic solvents may be combinatorially dispensed into the tubes using a multi-channel dispenser. Each tube in a 96-tube array is then sealed within 15 seconds of combinatorial dispensing to avoid solvent evaporation. The mixtures are then rendered supersaturated by heating to 70 degrees C for 2 hours followed by a 1 degree C/minute cooling ramp to 5 degrees C. Optical checks are then conducted to detect crystals and/or solid material. Once a solid has been identified in a tube, it is isolated through aspiration and drying. Raman spectra are then obtained on the solids and cluster classification of the spectral patterns is performed using proprietary software (Inquire™).

b) Crystallization from solution

Co-crystals may be obtained by dissolving the separate components in a solvent and adding one to the other. The co-crystal may then precipitate or crystallize as the solvent mixture is evaporated slowly. The co-crystal may also be obtained by dissolving the two components in the same solvent or a mixture of solvents.

c) Crystallization from the melt (Co-melting)

A co-crystal may be obtained by melting the two components together (i.e., co-melting) and allowing recrystallization to occur. In some cases, an anti-solvent may be added to facilitate crystallization.

d) Thermal microscopy

A co-crystal may be obtained by melting the higher melting component on a glass slide and allowing it to recrystallize. The second component is then melted and is also allowed to recrystallize. The co-crystal may form as a separated phase/band in between the eutectic bands of the two original components.

e) Mixing and/or grinding

A co-crystal may be obtained by mixing or grinding two components together in the solid state.

f) Co-sublimation

A co-crystal may be obtained by co-subliming a mixture of an API and a co-crystal former in the same sample cell as an intimate mixture either by heating, mixing or placing the mixture under vacuum. A co-crystal may also be obtained by co-sublimation using a Kneudsen apparatus where the API and the co-crystal former are contained in separate sample cells, connected to a single cold finger, each of the sample cells is maintained at the same or different temperatures under a vaccum atmosphere in order to co-sublime the two components onto the cold-finger forming the desired co-crystal.

<u>Analytical Methods</u>

Differential scanning calorimetric (DSC) analysis of the samples was performed using a Q1000 Differential Scanning Calorimeter (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/98/2000/NT, version 3.1E;Build 3.1.0.40 (2001 TA Instruments-Water LLC).

For the DSC analysis, the purge gas used was dry nitrogen, the reference material was an empty aluminum pan that was crimped, and the sample purge was 50 mL/minute.

DSC analysis of the sample was performed by placing the modafinil sample in an aluminum pan with a crimped pan closure. The starting temperature was typically 20 degrees C with a heating rate of 10 degrees C/minute, and the ending temperature was 200 degrees C. All reported DSC transitions represent the temperature of endothermic or exothermic transition at their respective peaks with an error of +/- 2 degrees C, unless otherwise indicated.

Thermogravimetric analysis (TGA) of samples was performed using a Q500 Thermogravimetric Analyzer (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (2001 TA Instruments-Water LLC). In addition, the analysis software used was Universal Analysis 2000 for Windows 95/98/2000/NT, version 3.1E;Build 3.1.0.40 (2001 TA Instruments-Water LLC).

For the TGA experiments, the purge gas used was dry nitrogen, the balance purge was 40 mL/minute N_2, and the sample purge was 60 mL/minute N_2.

TGA was performed on the sample by placing the modafinil sample in a platinum pan. The starting temperature was typically 20 degrees C with a heating rate of 10 degrees C/minute, and the ending temperature was 300 degrees C.

A powder X-ray diffraction (PXRD) pattern for the samples was obtained using a D/Max Rapid, Contact (Rigaku/MSC, The Woodlands, TX, U.S.A.), which uses as its control software RINT Rapid Control Software, Rigaku Rapid/XRD, version 1.0.0 (1999 Rigaku Co.). In addition, the analysis software used were RINT Rapid display software, version 1.18 (Rigaku/MSC), and JADE XRD Pattern Processing, versions 5.0 and 6.0 ((1995-2002, Materials Data, Inc.).

For the PXRD analysis, the acquisition parameters were as follows: source was Cu with a K line at 1.5406 Å; x-y stage was manual; collimator size was 0.3 mm; capillary tube (Charles Supper Company, Natick, MA, U.S.A.) was 0.3 mm ID; reflection mode was used; the power to the X-ray tube was 46 kV; the current to the X-ray tube was 40 mA; the omega-axis was oscillating in a range of 0-5 degrees at a speed of 1 degree/minute; the phi-axis was spinning at an angle of 360 degrees at a speed of 2 degrees/second; 0.3 mm collimator; the collection time was 60 minutes; the temperature

was room temperature; and the heater was not used. The sample was presented to the X-ray source in a boron rich glass capillary.

In addition, the analysis parameters were as follows: the integration 2-theta range was 2-60 degrees; the integration chi range was 0-360 degrees; the number of chi segments was 1; the step size used was 0.02; the integration utility was cylint; normalization was used; dark counts were 8; omega offset was 180; and chi and phi offsets were 0.

PXRD diffractograms were also acquired via the Bruker AXS D8 Discover X-ray Diffractometer. This instrument was equipped with GADDS™ (General Area Diffraction Detection System), a Bruker AXS HI-STAR Area Detector at a distance of 15.05cm as per system calibration[2], a copper source (Cu/K_α 1.54056Å), automated x-y-z stage, and 0.5mm collimator. The sample was compacted into pellet form and mounted on the x-y-z stage. A diffractogram was acquired under ambient conditiona at a powder setting of 40kV and 40mA in reflection mode while the sampleremained stationary. The exposure time was varied and specified for each sample. The diffractogram obtained underwent a spatial remapping procedure to account for the geometrical pincushion distortion of the area detector then integrated along chi from –118.8 to –61.8 degrees and 2-theta 2.1-37 degrees at a step size of 0.02 degrees with normalization set to bin normalize.

The relative intensity of peaks in a diffractogram is not necessarily a limitation of the PXRD pattern because peak intensity can vary from sample to sample, e.g., due to crystalline impurities. Further, the angles of each peak can vary by about +/- 0.1 degrees, preferably +/- 0.05. The entire pattern or most of the pattern peaks may also shift by about +/- 0.1 degree due to differences in calibration, settings, and other variations from instrument to instrument and from operator to operator.

For PXRD data herein, including Tables and Figures, each composition of the present invention may be characterized by any one, any two, any three, any four, any five, any six, any seven, or any eight or more of the 2 theta angle peaks. Any one, two, three, four, five, or six DSC transitions can also be used to characterize the compositions

of the present invention. The different combinations of the PXRD peaks and the DSC transitions can also be used to characterize the compositions.

Data for the co-crystals are shown in Table IV and in the Figures.

Example 1

Modafinil:Malonic acid Co-crystal (Form I)

Using a 250 mg/mL modafinil-acetic acid solution, malonic acid was dissolved on a hotplate (about 67 degrees C) at a 1:2 modafinil to malonic acid ratio. The mixture was dried under flowing nitrogen overnight. A powdery white solid was produced. After further drying for 1 day, acetic acid was removed (as determined by TGA) and the crystal structure, as determined by PXRD, remained the same. PXRD data for the modafinil:malonic acid (1:1) co-crystal are listed in Table IV, and the diffractogram is shown in Figure 1 (Data as collected). DSC showed an endothermic transition at 106.23 degrees C, and the thermogram is shown in Figure 2. TGA thermogram is shown in Figure 3. Figures 4A and 4B show a Raman spectrum of the modafinil:malonic acid co-crystal (Form I) and three Raman spectra of modafinil, malonic acid, and the co-crystal, respectively. Figures 5A and 5B show an IR spectrum of the modafinil:malonic acid co-crystal (Form I) and three IR spectra of modafinil, malonic acid, and the co-crystal, respectively. The modafinil:malonic acid Form I co-crystal can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 1 including, but not limited to, 5.00, 9.17, 10.08, 16.81, 18.26, 19.43, and 22.77 degrees 2-theta.

The modafinil:malonic acid co-crystal was also prepared by grinding the API and co-crystal former together. 2.50 g of modafinil was mixed with 1.01 g of malonic acid in a large mortar and pestle (malonic acid added in increments over 7 days with about a 1:1.05 ratio made on the first day and increments added over the next seven days which resulted in a 1:2 modafinil:malonic acid ratio). The mixture was ground for 45 minutes initially and 20 minutes each time more malonic acid was added. On the seventh day the mixture of co-crystal and starting components was heated in a sealed 20 mL vial at 80 degrees C for about 35 minutes to facilitate completion of the co-crystal formation. PXRD analysis of the resultant material was completed, and is shown in Figure 6

(background subtracted). The modafinil:malonic acid Form I co-crystal can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 6 including, but not limited to, 5.11, 9.35, 16.87, 18.33, 19.53, 22.05 and 22.89 degrees 2-theta. Single crystal data of the modafinil:malonic acid (Form I) co-crystal were acquired and are reported below. Figure 7 shows a packing diagram of the modafinil:malonic acid (Form I).

Crystal data: $C_{18}H_{19}NO_6S$, M = 377.40, monoclinic C2/c; a = 18.728(8) angstroms, b = 5.480(2) angstroms, c = 33.894(13) angstroms, alpha = 90 degrees, beta = 91.864(9) degrees, gamma = 90 degrees, T = 100(2) K, Z = 8, D_c = 1.442 Mg/m^3, U = 3477(2) cubic angstroms, λ = 0.71073 angstroms, 6475 reflections measured, 3307 unique (R_{int} = 0.1567). Final residuals were R_1 = 0.1598, wR_2 = 0.3301 for I>2sigma(I), and R_1 = 0.2544, wR_2 = 0.3740 for all 3307 data.

Example 2

Modafinil:Malonic acid Co-crystal (Form II)

A polymorph of the modafinil:malonic acid co-crystal of Example 1 was prepared in a vial. 11.4 mg of modafinil and 8.9 mg of malonic acid were dissolved in 2 mL of acetone. The solids dissolved at room temperature, and the vial was left open to evaporate the solvent in air. Large parallelogram shaped crystals formed on the walls and bottom of the vial. The PXRD diffractogram of the large crystals showed modafinil:malonic acid co-crystals Form II (See Figure 8, data as collected), a polymorphic form of modafinil:malonic acid Form I. The modafinil:malonic acid Form II co-crystal can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 8 including, but not limited to, 5.90, 9.54, 15.79, 18.02, 20.01, 21.66, and 22.47 degrees 2-theta.

Example 3

Modafinil:Glycolic acid Co-crystal

Modafinil (1 mg, 0.0037mmol) and glycolic acid (0.30 mg, 0.0037 mmol) were dissolved in acetone (400 microliters). The solution was allowed to evaporate to dryness

and the resulting solid was characterized using PXRD. PXRD data for the modafinil:glycolic acid co-crystal are listed in Table IV. See Figures 9A and 9B. Figure 9A shows the PXRD diffractogram after subtraction of background noise. Figure 9B shows the raw PXRD data as collected.

An alternative method for the preparation of modafinil:glycolic acid co-crystals was also completed. To a solution of modafinil (1 mg, 0.0037 mmol) dissolved in a mixture of acetone and methanol (3:1, 100 microliters) was added glycolic acid (0.28 mg, 0.0037 mmol) dissolved in methanol (50 microliters). The solvent was then evaporated to dryness under a flow of nitrogen to give a mixture of the two starting components. Acetone (200 microliters) was then added to the mixture and it was heated to 70 degrees C and maintained at 70 degrees C for 2 hours. The sample was then cooled to 5 degrees C and maintained at that temperature for 1 day. After 1 day, the cap was removed from the vial and the solvent was evaporated to dryness to give a 1:1 modafinil:glycolic acid co-crystal as a colorless solid. The modafinil:glycolic acid co-crystal was characterized by PXRD. The modafinil:glycolic acid co-crystal can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 9A including, but not limited to, 9.51, 14.91, 15.97, 19.01, 20.03, 21.59, 22.75, 25.03, and 25.71 degrees 2-theta. The modafinil:glycolic acid co-crystal can, likewise, be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 9B including, but not limited to, 9.53, 14.93, 15.99, 19.05, 20.05, 21.61, 22.77, and 25.05 degrees 2-theta.

Example 4

Modafinil:Maleic acid Co-crystal

Using a 250 mg/ml modafinil in acetic acid solution, maleic acid was dissolved on a hotplate (about 67 degrees C) at a 2:1 modafinil to maleic acid ratio. The mixture was dried under flowing nitrogen overnight. A clear amorphous material remained. Solids began to grow after 2 days stored in a sealed vial at room temperature. The resulting solid was characterized using PXRD (See Figures 10A and 10B). Figure 10A shows the PXRD diffractogram after subtraction of background noise. Figure 10B shows the raw

PXRD data. PXRD data for the modafinil:maleic acid co-crystal are listed in Table IV. The modafinil:maleic acid co-crystal can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 10A including, but not limited to, 4.69, 6.15, 9.61, 10.23, 15.65, 16.53, 17.19, 18.01, 19.97, 21.83, and 22.45 degrees 2-theta. The modafinil:maleic acid co-crystal can, likewise, be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 10B including, but not limited to, 4.69, 6.17, 9.63, 10.25, 15.67, 16.53, 17.21, 18.05, 19.99, 21.85, and 22.47 degrees 2-theta.

Example 5

Modafinil:L-tartaric acid Co-crystal

A modafinil:L-tartaric acid co-crystal was prepared by mixing 10.12 mg of modafinil and 5.83 mg of L-tartaric acid in 2 mL of methanol. All solids were dissolved at room temperature. The solution was then left to evaporate in air. The clear and viscous material was dried further under flowing nitrogen for 2 days, and then capped. After 6 days, a small amount of white solid formed. 1 day after the first solids are seen approximately 60 % of the remaining clear amorphous volume converted to the solid form. A sample of this material was analyzed by PXRD (See Figure 11). The modafinil:L-tartaric acid co-crystal can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 11 including, but not limited to, 6.10, 7.36, 9.38, 14.33, 16.93, 17.98, 18.81, 20.15, 20.71, 22.49, and 25.04 degrees 2-theta.

Example 6

Modafinil:Citric acid Co-crystal

Modafinil (25.3 mg, 93 mmol) and citric acid monohydrate (26.8 mg, 128 mmol) were ground together for 3 minutes. 1 mg of the resulting mixture was then dissolved in acetone (100 microliters) and heated to 70 degrees C and maintained at that temperature for 2 hours. The solution was then cooled to 5 degrees C and was left at that temperature for 2 days. After 2 days the cap was removed from the vial and one drop of water was added. The solvent was then evaporated to give a 1:1 modafinil:citric acid monohydrate

co-crystal as a colorless solid. The modafinil:citric acid monohydrate co-crystal was characterized by PXRD (See Figure 12, background subtracted). The modafinil:citric acid co-crystal can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 12 including, but not limited to, 5.29, 7.29, 9.31, 12.41, 13.29, 17.29, 17.97, 18.79, 21.37, and 23.01 degrees 2-theta.

Example 7

Modafinil:Succinic acid Co-crystal

Modafinil (25mg, 90 mmol) and succinic acid (10.6 mg, 90 mmol) were placed in a glass vial and dissolved in methanol (20 microliters). The resulting solution was heated at 70 degrees C for 2 hours and then cooled to 5 degrees C and maintained at that temperature for 2 days. After 2 days, the cap was removed from the vial and the solvent was evaporated at 65 degrees C to give a 1:1 modafinil:succinic acid co-crystal as a colorless solid. The modafinil:succinic acid co-crystal was characterized by PXRD and DSC. (See Figures 13A, 13B, and 14) Figure 13A shows the PXRD diffractogram after subtraction of background noise. Figure 13B shows the raw PXRD data. Figure 14 shows the DSC thermogram.

An alternative method for the preparation of modafinil:succinic acid co-crystals was also completed. 49.7 mg of modafinil and 21.6 mg of succinic acid was charged to a round bottom flask to make a 1:1 mixture. Add 1.5 mL of methanol and dissolve at 65 degrees C using a hot water bath. Seed crystals of modafinil:succinic acid co-crystal from the above preparation were added to the flask. The methanol was then evaporated using a rotary evaporator and a 65 degrees C hot water bath. PXRD of the collected solid confirms the synthesis of the modafinil:succinic acid co-crystal. The modafinil:succinic acid co-crystal can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 13A including, but not limited to, 5.45, 9.93, 15.85, 17.97, 18.73, 19.95, 21.33, 21.93, 23.01, and 25.11 degrees 2-theta. The modafinil:succinic acid co-crystal can, likewise, be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 13B

including, but not limited to, 5.45, 9.93, 15.87, 17.99, 18.75, 19.95, 21.95, 23.03, and 25.07 degrees 2-theta.

Example 8

R-(-)-Modafinil:Malonic acid Co-crystal

R-(-)-modafinil:malonic acid co-crystal was prepared by grinding R-(-)-modafinil (29.7 mg, 0.109 mmol) with malonic acid (11.9 mg, 0.114 mmol). The ground mixture was then heated to 80 degrees C for 10 minutes. The powder was analyzed by PXRD and DSC (See Figures 15 and 16, respectively). The PXRD pattern confirms that the co-crystal was made and shows many similarities to the PXRD pattern for the racemic modafinil:malonic acid co-crystal. The R-(-)-modafinil:malonic acid co-crystal can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 15 including, but not limited to, 5.04, 9.26, 16.73, 18.23, 19.37, 21.90, 22.74, 24.44, and 25.67 degrees 2-theta (data as collected). The DSC showed a melting peak at 111.59 degrees C with a heat of fusion of 112.9 J/g.

Example 9

R-(-)-Modafinil:Succinic acid Co-crystal

R-(-)-modafinil:succinic acid co-crystal was prepared by grinding R-(-)-modafinil (30.9 mg, 0.113 mmol) with succinic acid (14.8 mg, 0.125 mmol). The ground mixture was then heated to 145 degrees C for 5 minutes. The powder was analyzed by PXRD and DSC (See Figures 17 and 18, respectively). The PXRD pattern confirms that the co-crystal was made and shows many similarities to the PXRD pattern for the racemic modafinil:succinic acid co-crystal made from solution. The R-(-)-modafinil:succinic acid co-crystal can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 17 including, but not limited to, 5.36, 9.83, 15.80, 17.88, 18.70, 19.87, 21.21, 21.85, and 25.96 degrees 2-theta (data as collected). The DSC showed a melting peak at 143.4 degrees C with a heat of fusion of 140.7 J/g.

Example 10

R-(-)-Modafinil:Citric acid Co-crystal

R-(-)-modafinil:citric acid co-crystal was prepared by grinding R-(-)-modafinil (30.0 mg, 0.110 mmol) with citric acid monohydrate (27.1 mg, 0.129 mmol). The powder was analyzed by PXRD and DSC (See Figures 19 and 20, respectively). The PXRD pattern confirms that the co-crystal was made and shows many similarities to the PXRD pattern for the racemic modafinil:citric acid co-crystal. The R-(-)-modafinil:citric acid co-crystal can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 19 including, but not limited to, 5.18, 7.23, 9.23, 12.32, 13.23, 17.25, 17.92, 18.76, 20.25, 21.30, and 23.71 degrees 2-theta (data as collected). The DSC showed a melting peak at 111.59 degrees C with a heat of fusion of 112.9 J/g.

Table IV: Co-crystals of Modafinil

Co-Crystal former	**Representative PXRD Peaks** (degrees 2-theta)
Malonic acid (Form I)	5.00, 9.17, 10.08, 16.81, 18.26, 19.43, 22.77
Malonic acid (Form II)	5.90, 9.54, 15.79, 18.02, 20.01, 21.66, 22.47
Glycolic acid	9.53, 14.93, 15.99, 19.05, 20.05, 21.61, 22.77, 25.05
Maleic acid	4.69, 6.17, 9.63, 10.25, 15.67, 16.53, 17.21, 18.05, 19.99, 21.85, 22.47
L-tartaric acid	6.10, 7.36, 9.38, 14.33, 16.93, 17.98, 18.81, 20.15, 20.71, 22.49, 25.04
Citric acid	5.29, 7.29, 9.31, 12.41, 13.29, 17.29, 17.97, 18.79, 21.37, 23.01
Succinic acid	5.45, 9.93, 15.87, 17.99, 18.75, 19.95, 21.95, 23.03, 25.07
*Malonic acid	5.04, 9.26, 16.73, 18.23, 19.37, 21.90, 22.74, 24.44, 25.67
*Succinic acid	5.36, 9.83, 15.80, 17.88, 18.70, 19.87, 21.21, 21.85, 25.96
*Citric acid	5.18, 7.23, 9.23, 12.32, 13.23, 17.25, 17.92, 18.76, 20.25, 21.30, 23.71

* = API is R-(-)-modafinil, all other co-crystals comprise racemic modafinil

Example 11

Acetic acid Solvate of Modafinil

12.9 mg modafinil was mixed with 40 microliters acetic acid. The mixture was heated at 50 degrees C to completely dissolve the solid. The solution was allowed to cool to room temperature, and left overnight, which yielded no precipitation. The solution was then evaporated under flowing nitrogen until precipitation was observed. The resulting solid was further dried under flowing nitrogen. Characterization of the product has been achieved via PXRD, TGA, DSC, and Raman spectroscopy. (See Figures 21-24, respectively) An alternative method for the preparation of the acetic acid solvate of

modafinil was also completed. A sample of modafinil acetic acid solvate was prepared by dissolving 12.9 mg of the compound in 40 microliters acetic acid incubating at 65 degrees C for 30 minutes to dissolve, then cooling to 25 degrees C to incubate overnight. The sample was then evaporated to approximately 1/3 volume. After centrifugation of the sample, rapid nucleation and growth of crystals was observed. An additional 20 microliters of acetic acid was then added. The sample was heated at 50 degrees C until partial dissolution of the crystals was observed. The sample was then cooled to room temperature over a 1 hour period, then to 5 degrees C for 3 hours in an attempt to induce crystal growth. The sample was then dried under nitrogen gas. Rapid appearance of crystals was observed. The modafinil acetic acid solvate can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 21 including, but not limited to, 6.17, 9.63, 15.69, 17.97, 19.99, and 21.83 degrees 2-theta (data as collected).

Example 12

Tetrahydrofuran Solvate of Modafinil

The tetrahydrofuran (THF) solvate of modafinil was prepared by placing 10.4 mg of modafinil in 1 mL of tetrahydrofuran. The powder submerged in the tetrahydrofuran did not completely dissolve and was observed to convert, overnight, into long, fine, needle shaped crystals which were collected and analyzed by PXRD (See Figure 25). The modafinil tetrahydrofuran solvate can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 25 including, but not limited to, 6.97, 9.79, 10.97, 16.19, 19.03, 19.71, 20.59, 22.25, and 25.13 degrees 2-theta (data as collected).

Example 13

1,4-Dioxane Solvate of Modafinil

The 1,4-dioxane solvate of modafinil was prepared by placing 11.6 mg of modafinil in 1 mL of 1,4-dioxane. The powder submerged in the 1,4-dioxane was observed to convert, overnight, into long fine needle shaped crystals which were

collected and analyzed by PXRD (See Figure 26). The modafinil 1,4-dioxane solvate can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 26 including, but not limited to, 6.93, 9.85, 10.97, 16.19, 18.97, 19.61, 20.33, 20.65, and 22.07 degrees 2-theta (data as collected).

Example 14

Methanol Solvate of Modafinil

The methanol solvate of modafinil is obtained by evaporating 2 mL of a 30 mg/mL modafinil solution in methanol under flowing nitrogen overnight. The methanol solvate was characterized by PXRD, TGA, and DSC (See Figures 27, 28, and 29, respectively). The modafinil methanol solvate can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 27 including, but not limited to, 6.15, 9.89, 12.25, 15.69, 17.97, 20.07, 21.85, and 22.73 degrees 2-theta (data as collected).

Example 15

Nitromethane Solvate of Modafinil

The nitromethane solvate of modafinil was prepared by placing 12.9 mg of modafinil in 1 mL of nitromethane. The powder submerged in the nitromethane did not completely dissolve and was observed to coarsen, overnight, forming large rectangular crystals. The solid was collected and analyzed by PXRD (See Figure 30). The modafinil nitromethane solvate can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 30 including, but not limited to, 6.17, 9.77, 15.89, 18.11, 20.07, 22.17, 22.91, 25.31, and 25.83 degrees 2-theta (data as collected).

Example 16

Modafinil (1 mg, 0.0037mmol) and mandelic acid (0.55 mg, 0.0037 mmol) were dissolved in acetone (400 microliters). The solution was allowed to evaporate to dryness and the resulting solid was characterized using PXRD (See Figure 31). The obtained solid may be a solvate of modafinil. The form can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 31 including, but

not limited to, 6.11, 9.53, 14.77, 15.77, 18.03, 20.01, and 21.61 degrees 2-theta (background removed).

Example 17

Modafinil (1 mg, 0.0037mmol) and fumaric acid (0.42 mg, 0.0037 mmol) were dissolved in 1,2-dichloroethane (400 microliters). The solution was allowed to evaporate to dryness and the resulting solid was characterized using PXRD (See Figure 32). The obtained solid may be a solvate of modafinil. The form can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 32 including, but not limited to, 5.87, 8.95, 12.49, 13.99, 18.19, 19.99, 21.57, and 25.01 degrees 2-theta (background removed).

Example 18

Polymorph of Modafinil

Modafinil was dispensed from a stock solution containing 50 mg of modafinil in 20 mL of a 15:5 acetone/methanol mixture. The solution was then evaporated to dryness under a flow of nitrogen. Mandelic acid was dispensed from an acetone solution and the mixture was again evaporated to dryness. 200 microliters of acetone was then added and the vials were capped. After standing at room temperature for one day, the caps were removed and the solvent was allowed to evaporate. PXRD was carried out on the sample (See Figure 33). The modafinil polymorph is denoted as form VII. The polymorph (form VII) can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 33 including, but not limited to, 5.47, 9.99, 15.73, 17.85, 18.77, 20.05, 21.23, 22.05, 23.15, and 25.13 degrees 2-theta (data as collected).

Example 19

Modafinil:Malonic acid Co-Crystal Pharmacokinetic Study in Dogs

The modafinil:malonic acid co-crystal (from Example 1) was administered to dogs in a pharmacokinetic study. Particles of modafinil:malonic acid co-crystal with a median particle size of about 16 micrometers were administered in the study. As a reference,

micronized modafinil with a median particle size of about 2 micrometers was also administered in the study. The AUC of the modafinil:malonic acid co-crystal was determined to be 40 to 60 percent higher than that of the pure modafinil. Such a higher bioavailability illustrates the modulation of an important pharmacokinetic parameter due to an embodiment of the present invention. A compilation of important pharmacokinetic parameters measured during the animal study are included in Table V.

Table V- Pharmacokinetic parameters of modafinil:malonic acid co-crystal and pure modafinil in dogs

Parameter	Pure Modafinil	Modafinil:malonic acid co-crystal
Median particle size	2 micrometers	16 micrometers
C_{max} (ng/mL)	11.0 ± 5.9	10.3 ± 3.4
T_{max} (hours)	1.3 ± 0.6	1.7 ± 0.6
AUC (relative)	1.0	1.4-1.6
Half-life (hours)	2.1 ± 0.7	5.1 ± 2.4

The increased half-life and bioavailability of modafinil in the malonic acid co-crystal may be due to the presence of malonic acid. It is believed that the malonic acid may be inhibiting one or more pathways responsible for the metabolism or elimination of modafinil. It is noted that modafinil and malonic acid share a similar structure: each including two carbonyl or sulfonyl groups separated by a $-CH_2-$ and each molecule is terminated with a group that is capable of participation in a hydrogen bond with an enzyme. Such a mechanism may take place with other APIs or co-crystal formers of similar structure.

Example 20

Modafinil:Malonic acid Co-crystal Solid-State Stability

The stability of the modafinil:malonic acid co-crystal was measured at various temperatures and relative humidities over a four week period. No degradation was found to occur at 20 or 40 degrees C. At 60 degrees C, about 0.14 percent degradation per day was determined based on a simple exponential model. At 80 degrees C, about 8 percent degradation per day was determined.

Example 21

Formulation of Modafinil:Malonic Acid Co-crystal

The formulation of a modafinil:malonic acid co-crystal was completed using lactose. Two mixtures, one of modafinil and lactose, and the second of modafinil:malonic acid co-crystal and lactose, were ground together in a mortar an pestle. The mixtures targeted a 1:1 weight ratio of modafinil to lactose. In the modafinil and lactose mixture, 901.2 mg of modafinil and 901.6 mg of lactose were ground together. In the modafinil:malonic acid co-crystal and lactose mixture, 1221.6 mg of co-crystal and 871.4 mg of lactose were ground together. The resulting powders were analyzed by PXRD and DSC. The PXRD patterns and DSC thermograms of the mixtures showed virtually no change upon comparison with both individual components. The DSC of the co-crystal mixture showed only the co-crystal melting peak at 113.6 degrees C with a heat of fusion of 75.9 J/g. This heat of fusion is 59.5 % of that found for the co-crystal alone (127.5 J/g). This result is consistent with a 58.4 % weight ratio of co-crystal in the mixture. The DSC of the modafinil and lactose mixture had a melting point of 165.7 degrees C. This is slightly lower then the measured melting point of modafinil (168.7 degrees C). The heat of fusion of the mixture (59.3 J/g) is 46.9 % that of the modafinil alone (126.6 J/g), which is consistent with the estimated value of 50 %.

The *in vitro* dissolution of both the modafinil:malonic acid co-crystal and pure modafinil were tested in capsules. Both gelatin and hydroxypropylmethyl cellulose (HPMC) capsules were used in the dissolution study. The capsules were formulated with and without lactose. All formulations were ground in a mortar and pestle prior to transfer into a capsule. The dissolution of the capsules was tested in 0.01 M HCl (See Figure 34).

In 0.01N HCl, using sieved and ground materials in gelatin capsules:

Modafinil and the modafinil:malonic acid co-crystal were passed through a 38 micrometer sieve. Gelatin capsules (Size 0, B&B Pharmaceuticals, Lot # 15-01202) were filled with 200.0 mg sieved modafinil, 280.4 mg sieved modafinil:malonic acid co-crystal, 200.2 mg ground modafinil, or 280.3 mg ground modafinil:malonic acid co-crystal. Dissolution studies were performed in a Vankel VK 7000 Benchsaver Dissolution Testing Apparatus with the VK750D heater/circulator set at 37 degrees C. At

0 minutes, the capsules were dropped into vessels containing 900 mL 0.01 M HCl and stirred by paddles.

Absorbance readings were taken using a Cary 50 Spectrophotometer (wavelength set at 260nm) at the following time points: 0, 5, 10, 15, 20, 25, 30, 40, 50, and 60 minutes. The absorbance values were compared to those of standards and the modafinil concentrations of the solutions were calculated.

In 0.01N HCl, using ground materials in gelatin or HPMC capsules, with and without lactose:

Modafinil and the modafinil:malonic acid co-crystal were mixed with equivalent amounts of lactose (Spectrum, Lot QV0460) for approximately 5 minutes. Gelatin capsules (Size 0, B&B Pharmaceuticals, Lot # 15-01202) were filled with 400.2 mg modafinil and lactose (approximately 200 mg modafinil), or 561.0 mg modafinil:malonic acid co-crystal and lactose (approximately 200 mg modafinil). HPMC capsules (Size 0, Shionogi, Lot # A312A6) were filled with 399.9 mg modafinil and lactose, 560.9 mg modafinil:malonic acid co-crystal and lactose, 199.9 mg modafinil, or 280.5 mg modafinil:malonic acid co-crystal. The dissolution study was carried out as described above.

Example 22

Polymorphs of R-(-)-modafinil

Four polymorphs of R-(-)-modafinil have been observed, each characterized by PXRD. Figures 35, 36, 37, and 38 shows these PXRD diffractograms (data as collected) of polymorphs Form I, Form II, Form III, and Form IV, respectively. The polymorph form I characterized in Figure 35 has a melting point of about 166.8 degrees C as determined by DSC. Form I can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 35 including, but not limited to, 8.97, 10.15, 12.87, 14.15, 15.13, 15.77, 18.18, and 20.39 degrees 2-theta (data as collected). Form II can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 36 including, but not limited to, 7.21, 10.37, 17.73, 19.23, 21.17, 21.77 and 23.21 degrees 2-theta (data as collected). Form III

can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 37 including, but not limited to, 6.61, 10.39, 13.99, 16.49, 17.73, 19.03, 20.87 and 22.31 degrees 2-theta (data as collected). Form IV can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 38 including, but not limited to, 7.79, 10.31, 11.77, 16.49, 17.33, 19.47, and 23.51 degrees 2-theta (data as collected).

TABLE I

Table I

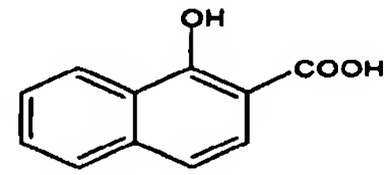
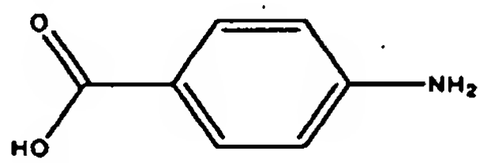
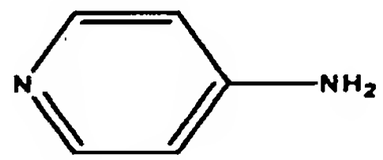
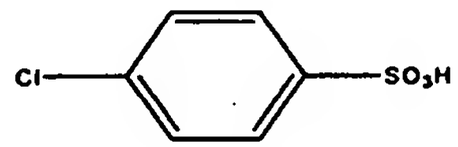
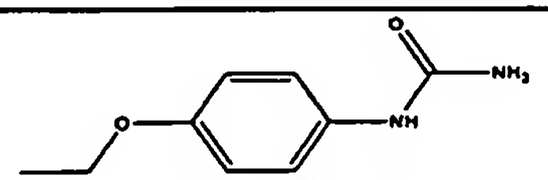
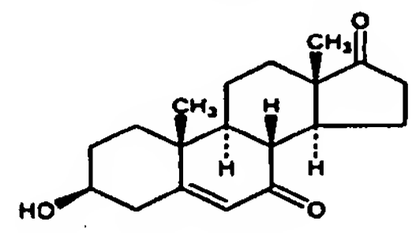
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
1-Hydroxy-2-naphthoic acid	188.18	191-192	2	Carboxylic acid, alcohol	1	2		2.7, 13.5
4-aminobenzoic acid	137.14	187-188	2	Amine, carboxylic acid	1	3		4.7, 4.8
4-aminopyridine	94.11	158-159	3	Amine, pyridine	1	2		10
4-Chlorobenzene-sulfonic acid	192.63	67	1	SO_3H	3	1		0-1
4-ethoxyphenyl urea	180.2	173-174	3	Amide, NH	2	3		~7-9
7-oxo-DHEA	303	190-192	1	Alcohol, Ketone	3	1		

TABLE I

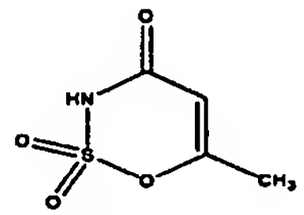
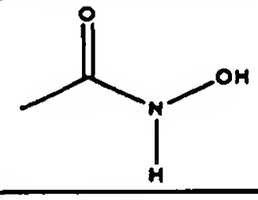
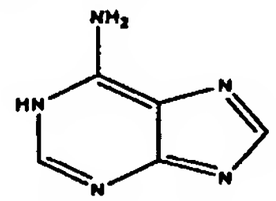
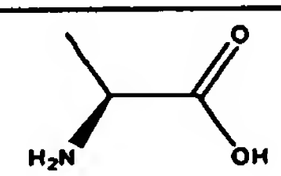
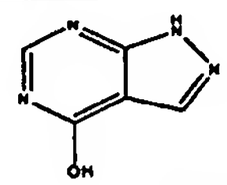
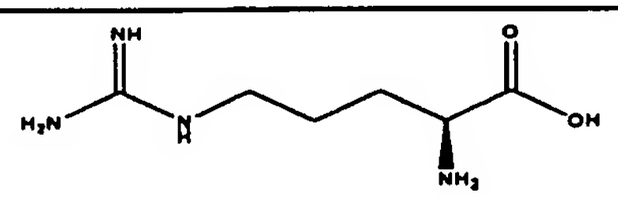
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Acesulfame	163.15	123-124	3	SO_2, Amide	4	1		~5-7
Acetohydroxamic acid	75.07	89-92	3	Amide, NH, OH	2	2		8.7
Adenine	135.13	220 (sub.)	1	Amine, NH	3	3		3.8
Adipic Acid	146.14	152	1	Carboxylic acid	2	2	$HOOC(CH_2)_4COOH$	4.44, 5.44
Alanine	89.09	289-291	1	Amine, carboxillic acid	1	3		2.35, 9.87
Allopurinaol	136.11	> 350	3	OH, NH	4	2		10.2
Arginine	174.2	244 (dec.)	1	Amine, COOH	2	7		2.18, 9.09, 13.2

TABLE I

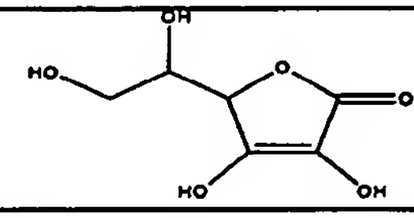
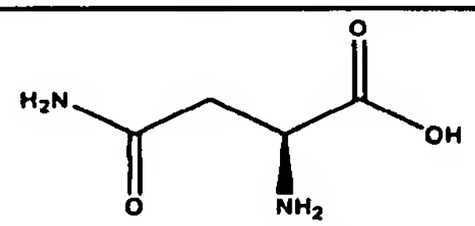
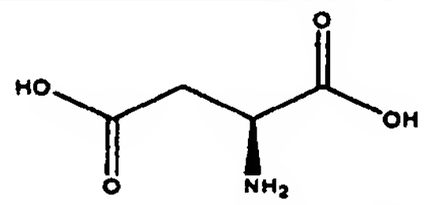
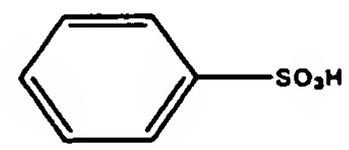
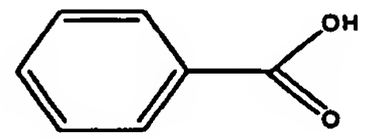
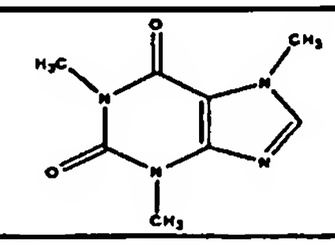
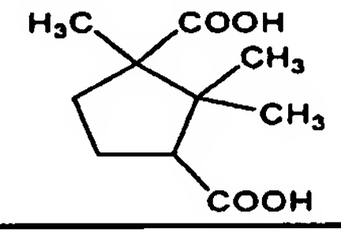
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Ascorbic acid	176.12	190-192	1	C=O, OH	6	4		4.17, 11.57
Asparagine	132.12	234-235	1	Amine, amide, COOH	3	5		2.02, 8.5
Aspartic acid	133.1	270-271	1	Amine, COOH	2	4		1.88, 3.65, 9.60
Benzenesulfonic Acid	158.18	43-44	1	SO_3H	2	1		0.70, 1.58
Benzoic acid*	122.12	122-123	2	COOH	1	1		4.19
Caffeine	194.19	238	3	C=O	3	0		
Camphoric acid	200.23	186-189	2	Carboxylic acid	2	2		4.72, 5.83

TABLE I

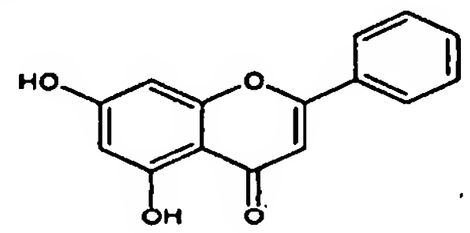
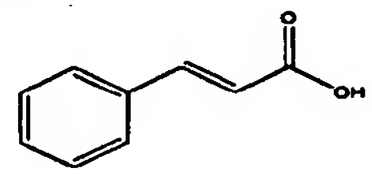
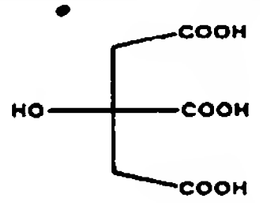
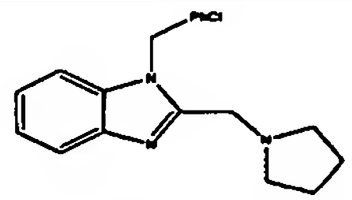
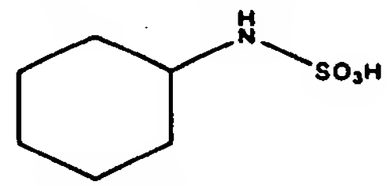
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Capric acid	172.27	31.4	1	Carboxylic acid	1	1	$CH_3(CH_2)_8COOH$	4.9
Chrysin	254.24	285	1	Phenol, ether, ketone	2	2		
Cinnamic acid	144.2	133	3	Carboxylic acid	1	1		4.4
Citric Acid	192.12	153	1	OH, COOH	4	4		3.13, 4.76, 6.40
Clemizole	325.84	167	1	Pyrrolidine	3	0		
Cyclamic acid	179.24	169-170	3	NH, SO_3H	2	2		-2

TABLE I

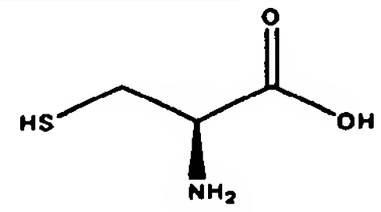
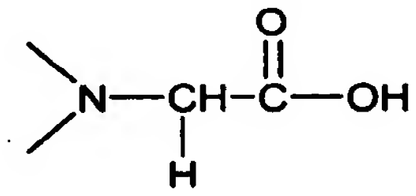
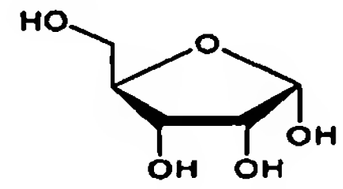
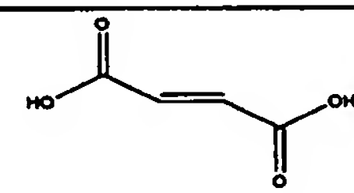
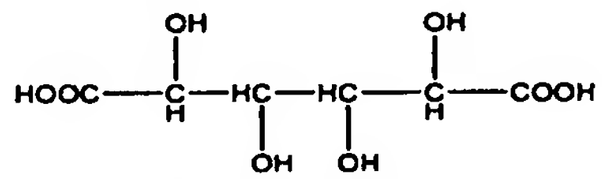
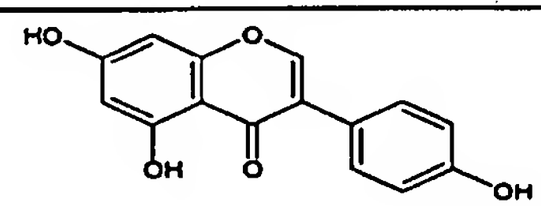
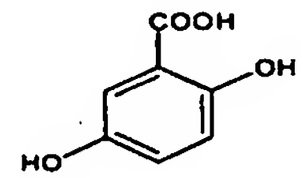
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Cysteine	121.15	---	1	Amine, COOH, SH	2	4		1.71, 8.33, 10.78
Dimethylglycine	103.1	178-192	1	Amine, Carboxylic acid	2	1		2.5
D-Ribose	150.13	87	1	Alcohol, ether	1	4		
Fumaric acid	116.07	287	1	COOH	2	2		3.03, 4.38
Galactaric acid	210.14	255 (dec)	1	Carboxylic acid, alcohol	2	6		3.08, 3.63
Genistein	270.24	297-298	1	Alcohol, Phenol, ether, ketone	2	3		
Gentisic acid	154.12	199-200 form I, 205 form II	2	Carboxylic acid, alcohol, phenol	1	3		2.93

TABLE I

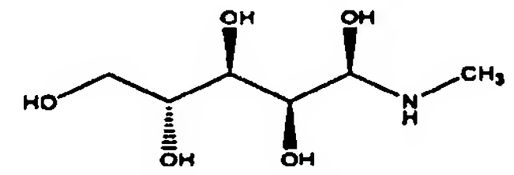
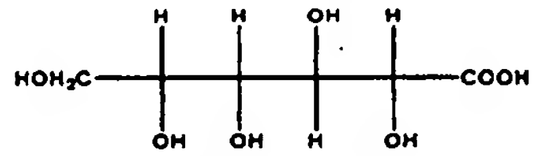
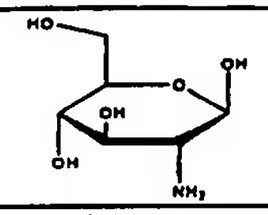
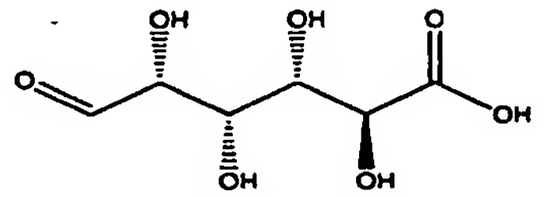
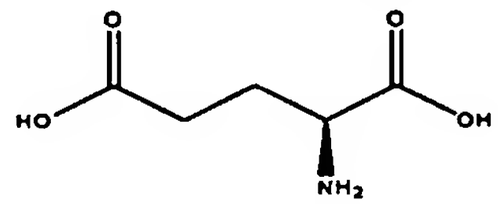
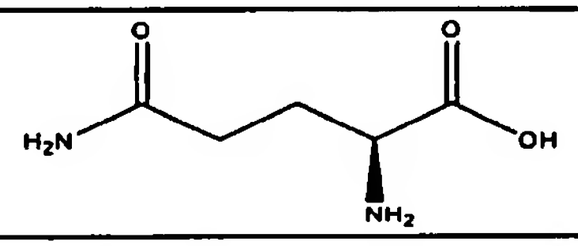
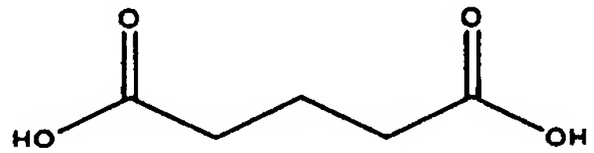
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Glucamine, N-Methyl	195.22	128-129	1	Alcohol, Amine	5	6		8.03(B)
Gluconic acid	196.15	131	1	OH, COOH	6	6		3.76
Glucosamine	179.17	88	1	OH	5	6		6.91
Glucuronic acid	194.14	165	1	Carboxylic acid, alcohol, aldehyde	2	5		3.18
Glutamic acid	147.13	160	1	Amine, COOH	2	4		2.19, 4.25, 9.67
Glutamine	146.15	185-186	1	Amine, Amide, COOH	2	5		2.17, 9.13
Glutaric acid	132.11	98-98	1	COOH	2	2		2.7, 4.5

TABLE I

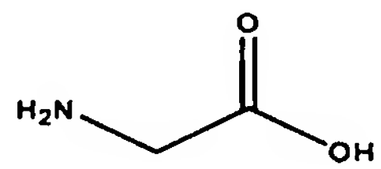
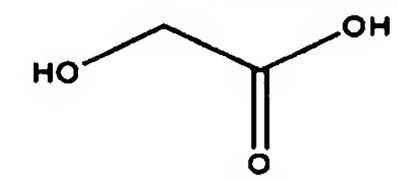
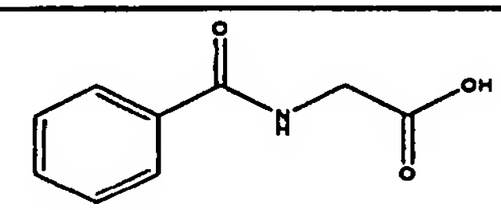
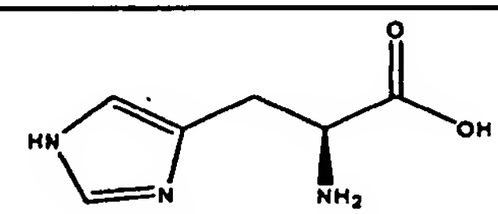
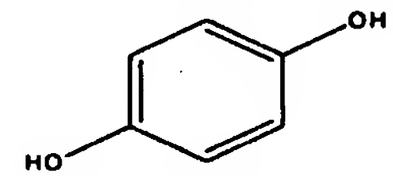
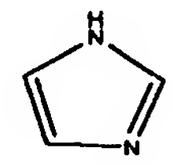
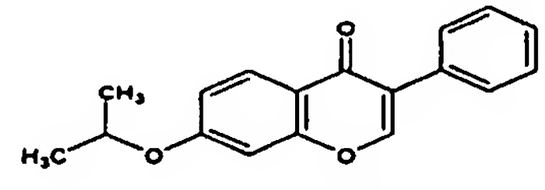
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Glycine	75.07	182	1	Amine, COOH	2	3		2.34, 9.6
Glycolic acid	76.05	80	1	OH, COOH	2	2		3.82
Hippuric acid	179.17	187-188	1	Amide, NH, COOH	2	2		3.55
Histidine	155.16	287 (dec.)	1	Amine, COOH, Imidazole	2	4		1.78, 5.97, 8.97
Hydroquinone*	110.11	170-171	2	OH, Phenol	2	2		~10
Imidazole	68.08	90-91	1	NH	1	1		6.92
Ipriflavone	280.32	115-117	1	Ketone, ether	3	0		

TABLE I

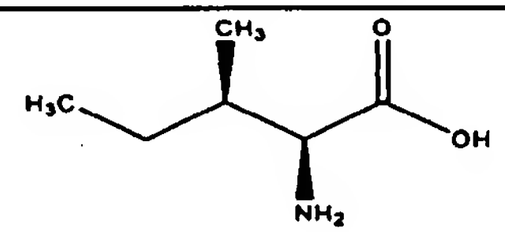
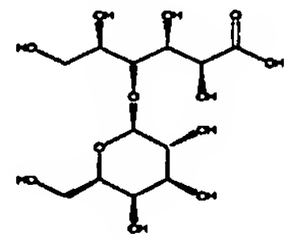
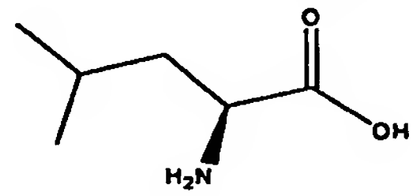
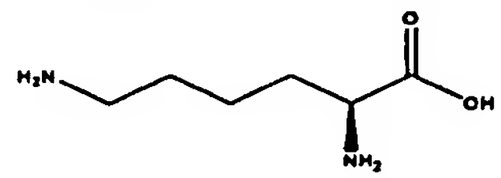
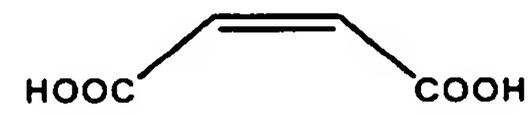
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Isoleucine	131.17	168-170 (sub.)	1	Amine, COOH	1	3		2.32, 9.76
Lactobionic acid	358.3	128-130	2	Alcohol, carboxylic acid, ether	1	9		3.2
Lauric acid	200.32	44-48	1	Carboxylic acid	1	1	$CH_3(CH_2)_{10}COOH$	~4.5
Leucine	131.17	145-148 (sub.)	1	Carboxylic acid, amine	1	3		2.36, 9.6
Lysine	146.19	225 (dec.)	1	Amine, COOH	1	5		2.2, 8.9, 10.28
Maleic	116.07	138-139	1	COOH	2	2		1.92, 6.23

TABLE I

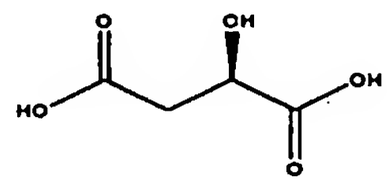
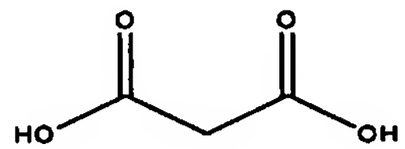
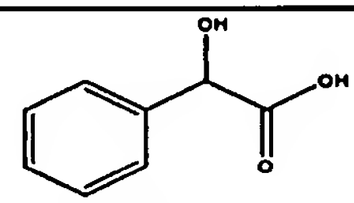
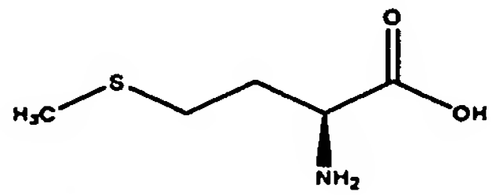
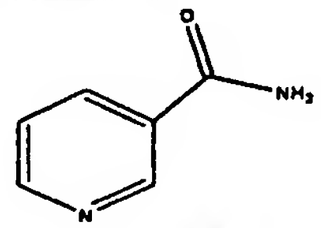
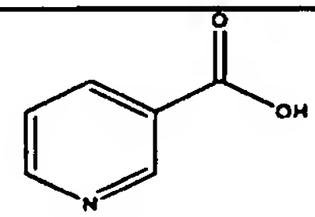
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Malic acid	134.09	131-132	1	OH, COOH	3	3		3.46, 5.1
Malonic	104.06	135	1	COOH	2	2		2.83, 5.70
Mandelic acid	152.15	119	1	OH, COOH	2	2		3.37
Methionine	149.21	280-282 (dec.)	1	Amine, COOH, S-Me	2	3		2-3, 9
Nicotinamide	122.12	128-131	1	Pyridine, amide	2	2		3.3
Nicotinic acid	123.11	236-237	2	Carboxylic acid, pyridine	2	1		2.07(B), 4.85

TABLE I

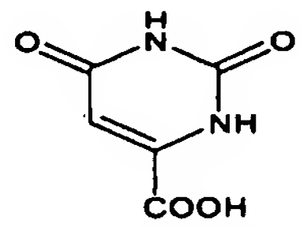
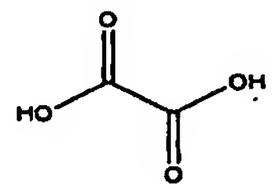
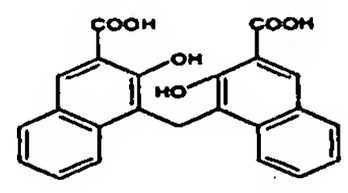
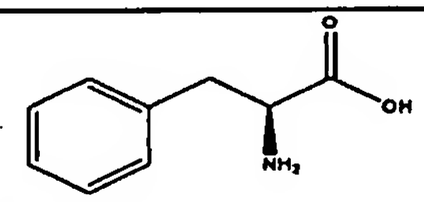
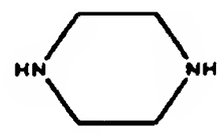
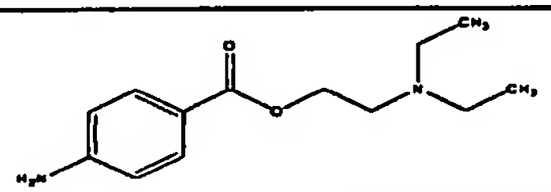
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Orotic acid	156.1	345-346	2	Carboxilic acid, lactam	3	3		5.85, 8.95
Oxalic acid	90.04	189 (dec)	2	Carboxilic acid	2	2		1.27, 4.27
Palmitic acid	256.43	63-64	1	Carboxylic acid	1	1	$CH_3(CH_2)_{14}COOH$	4.9
Pamoic	388.38	280 (dec)	2	Carboxylic acid, phenol	2	4		2.51, 3.1
Phenylalanine	165.19	283 (dec.)	1	Amine, COOH	1	3		~2, ~9
Piperazine	86.14	106	1	NH	0	2		9.82(B)
Procaine	236.31	61	1	Amine, C=O	2	2		8.9(B)

TABLE I

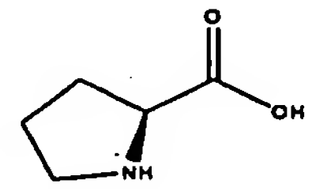
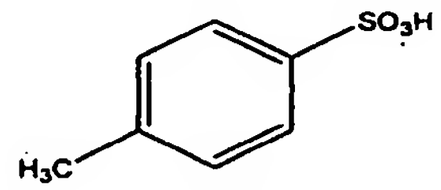
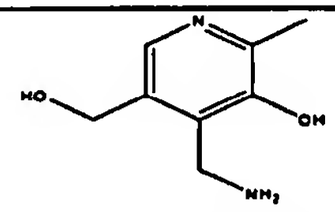
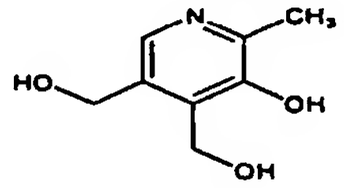
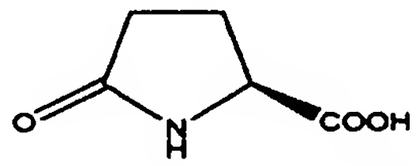
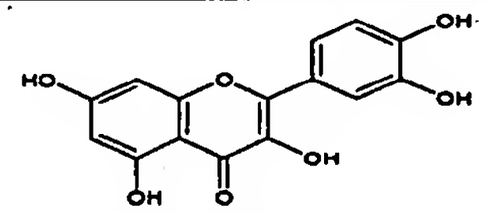
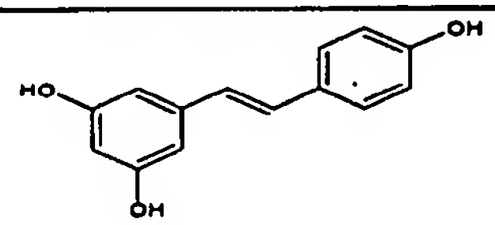
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Proline	115.13	220-222 (dec.)	1	COOH, NH	1	2		1.99, 10.6
p-Toluenesulfonic acid	172.2	106-107	2	Sulfonic acid	2	1		-1.34
Pyridoxamine	168	193-194	2	OH, Amine, Pyridine	3	4		~9
Pyridoxine	170	160	2	Alcohol, Pyridine	3	3		~9
Pyroglutamic acid	129.12	162	2	Carboxylic acid, Lactam	2	2		3.32
Quercetin	302.24	314 dec.	1	Phenol, ether, ketone	2	5		
Resveratrol	228.24	253-255	1	Phenol	0	3		

TABLE I

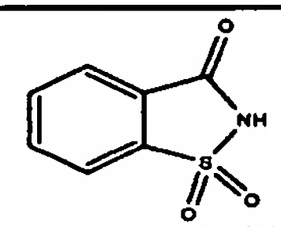
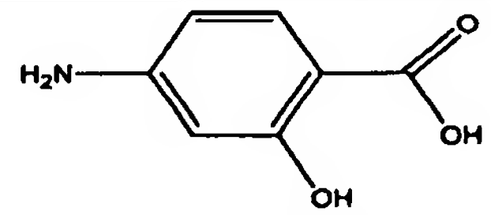
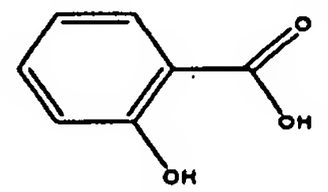
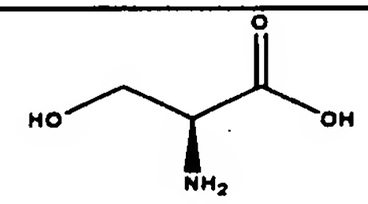
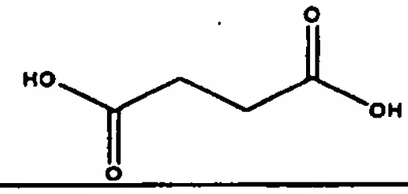
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Saccharin	183.19	228-230	1	Amide, C=O, S=O, N-H	3	1		2
Salicylic acid, 4-amino	153.14	150-151	3	COOH, OH, Analine	1	4		3.25, 10, 3.5(B)
Salicylic acid	138.12	159	3	COOH, OH	2	2		2.98, 13.82
Sebacic acid	202.25	134.5	1	Carboxylic acid	2	2	$HOOC(CH_2)_8COOH$	4.59, 5.59
Serine	105.09	228 (dec.)	1	Carboxylic acid, amine, OH	2	3		2.21, 9.15
Stearic acid	284.47	70-71	1	Carboxylic acid	1	1	$CH_3(CH_2)_{16}COOH$	4.9
Succinic acid	118.09	185-187	1	Carboxylic acid	2	2		4.21, 5.64

TABLE I

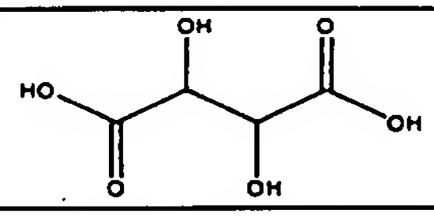
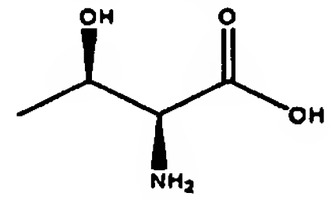
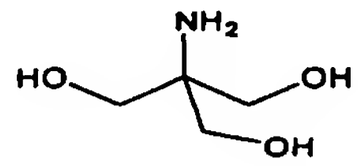
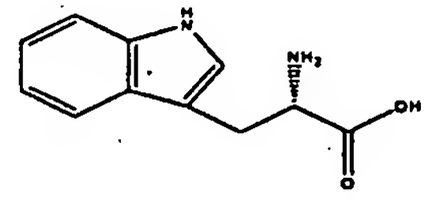
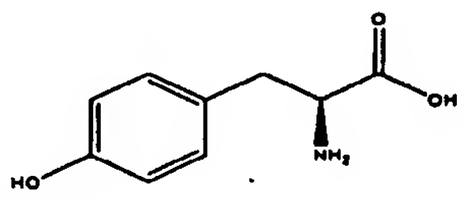
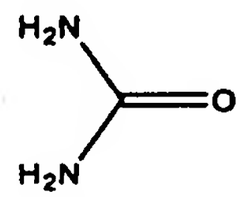
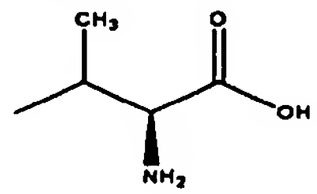
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Tartaric acid	150.09	205-206	1	Carboxylic acid	4	4		3.02, 4.36
Threonine	119.12	255-257 (dec.)	1	Amine, COOH, OH	2	4		2.15, 9.12
TRIS	121.13	171-172	2	Amine, OH	3	5		5.91, 8.3
Tryptophan	204.23	289 (dec.)	1	Amine, COOH, Indole	1	4		2.38, 9.39
Tyrosine	181.19	342-344	1	Amine, COOH, OH	2	3		2.2, 9.11, 10.07
Urea	60.06	Dec.	1	C=O, NH2	1	4		~8
Valine	117.15	315	1	Amine, COOH	1	3		~4.5, ~9

TABLE I

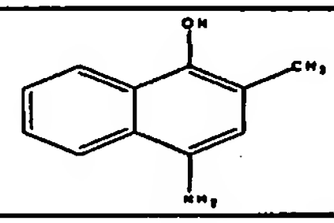
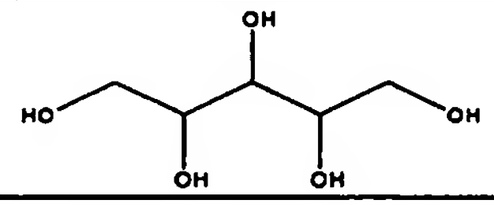
Co-Crystal Former	MW (g/mol)	MP (°C)	Class	Functionality	# acceptors	# donors	Molecular Strucutre	pKa Values
Vitamin K5	209.68	280-282 (dec.)	3	Amine, OH	1	3		~9
Xylitol	152.15	93-95 (I)	2	OH	5	5		~9

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group					
1,5-Napthalene-disulfonic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide
1-Hydroxy-2-naphthoic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
1-Hydroxy-2-naphthoic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine
4-Aminobenzoic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine
4-Aminobenzoic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
4-aminopyridine	Amine	alcohol	ketone	thiol	amide	amine	analine
4-aminopyridine	Pyridine	*alcohol	pyridinium	*	*amide	nitro	*amine
4-Chlorobenzene-Sulfonic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide
4-ethoxyphenyl Urea	Amide	alcohol	ketone	thiol	amide	amine	analine
4-ethoxyphenyl Urea	Amine	alcohol	ketone	thiol	amide	amine	analine
7-oxo-DHEA	alcohol	alcohol	ketone	thiol	amide	amine	analine
7-oxo-DHEA	Ketone	alcohol		thiol	amide	amine	analine
Acesulfame	Sulfone	pyridine	ketone	aldehyde	ether	ester	amide
Acesulfame	Amide	alcohol	ketone	thiol	amide	amine	analine
Acetohydroxamic Acid	Amide	alcohol	ketone	thiol	amide	amine	analine
Acetohydroxamic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine
Acetohydroxamic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Adenine	Amine	alcohol	ketone	thiol	amide	amine	analine
Adenine	N	*alcohol	pyridinium	*	*amide	nitro	*amine
Adipic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Alanine	Amine	alcohol	ketone	thiol	amide	amine	analine
Alanine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Allopurinaol	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Allopurinaol	Amine	alcohol	ketone	thiol	amide	amine	analine
Arginine	Amine	alcohol	ketone	thiol	amide	amine	analine
Arginine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Ascorbic Acid	Ketone	alcohol		thiol	amide	amine	analine
Ascorbic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Ascorbic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Asparagine	Amine	alcohol	ketone	thiol	amide	amine	analine

TABLE II

Co-crystal Former								
1,5-Napthalene-disulfonic Acid	Carboxylic Acid	amine	metals	thioether		sulfate	alcohol	
1-Hydroxy-2-naphthoic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals
1-Hydroxy-2-naphthoic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals
4-Aminobenzoic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
4-Aminobenzoic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
4-aminopyridine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
4-aminopyridine	*Carboxylic Acid	*sulfonamide	*ketone	ether	triazole		ammonium	oxime
4-Chlorobenzene-Sulfonic Acid	Carboxylic Acid	amine	metals	thioether		sulfate	alcohol	
4-ethoxyphenyl Urea	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
4-ethoxyphenyl Urea	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
7-oxo-DHEA	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals
7-oxo-DHEA	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Acesulfame	carboxilic acid	amine	metals	thioether		sulfate	alcohol	
Acesulfame	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Acetohydroxamic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Acetohydroxamic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Acetohydroxamic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Adenine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Adenine	*carboxilic acid	*sulfonamide	*ketone	ether	triazole		ammonium	oxime
Adipic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Alanine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Alanine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Allopurinaol	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Allopurinaol	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Arginine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Arginine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Ascorbic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Ascorbic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Ascorbic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Asparagine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid

TABLE II

Co-crystal Former								
1,5-Napthalene-disulfonic Acid								
1-Hydroxy-2-naphthoic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
1-Hydroxy-2-naphthoic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
4-Aminobenzoic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
4-Aminobenzoic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
4-aminopyridine	metals	aldehyde	ester	ether	cyano		furan	bromine
4-aminopyridine	*chlorine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone
4-Chlorobenzene-Sulfonic Acid								
4-ethoxyphenyl Urea	metals	aldehyde	ester	ether	cyano		furan	bromine
4-ethoxyphenyl Urea	metals	aldehyde	ester	ether	cyano		furan	bromine
7-oxo-DHEA	aldehyde	ester	ether	cyano		furan	bromine	chlorine
7-oxo-DHEA	metals	aldehyde	ester	ether	cyano		furan	bromine
Acesulfame								
Acesulfame	metals	aldehyde	ester	ether	cyano		furan	bromine
Acetohydroxamic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Acetohydroxamic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Acetohydroxamic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Acetohydroxamic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Adenine	metals	aldehyde	ester	ether	cyano		furan	bromine
Adenine	*chlorine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone
Adipic acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Alanine	metals	aldehyde	ester	ether	cyano		furan	bromine
Alanine	metals	aldehyde	ester	ether	cyano		furan	bromine
Allopurinaol	metals	aldehyde	ester	ether	cyano		furan	bromine
Allopurinaol	metals	aldehyde	ester	ether	cyano		furan	bromine
Arginine	metals	aldehyde	ester	ether	cyano		furan	bromine
Arginine	metals	aldehyde	ester	ether	cyano		furan	bromine
Ascorbic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Ascorbic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Ascorbic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Asparagine	metals	aldehyde	ester	ether	cyano		furan	bromine

TABLE II

Co-crystal Former						
1,5-Napthalene-disulfonic Acid						
1-Hydroxy-2-naphthoic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester
1-Hydroxy-2-naphthoic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester
4-Aminobenzoic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
4-Aminobenzoic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
4-aminopyridine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
4-aminopyridine	thiocyanate	*bromine		hydroxamic acid	cyano	carboxamide
4-Chlorobenzene-Sulfonic Acid						
4-ethoxyphenyl Urea	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
4-ethoxyphenyl Urea	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
7-oxo-DHEA	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester
7-oxo-DHEA	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Acesulfame						
Acesulfame	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Acetohydroxamic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Acetohydroxamic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Acetohydroxamic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Adenine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Adenine	thiocyanate	*bromine		hydroxamic acid	cyano	carboxamide
Adipic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Alanine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Alanine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Allopurinaol	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Allopurinaol	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Arginine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Arginine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Ascorbic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Ascorbic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Ascorbic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Asparagine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone

TABLE II

Co-crystal Former								
1,5-Napthalene-disulfonic Acid								
1-Hydroxy-2-naphthoic acid		fluorine	carbamate	imidazole	BF4			
1-Hydroxy-2-naphthoic acid		fluorine	carbamate	imidazole	BF4			
4-Aminobenzoic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
4-Aminobenzoic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
4-aminopyridine	phosphate ester		fluorine	carbamate	imidazole	BF4		
4-aminopyridine	*sulfonic acid	*phosphoric acid	N-oxide	ester	ether	fluorine	acetate	thione
4-Chlorobenzene-Sulfonic Acid								
4-ethoxyphenyl Urea	phosphate ester		fluorine	carbamate	imidazole	BF4		
4-ethoxyphenyl Urea	phosphate ester		fluorine	carbamate	imidazole	BF4		
7-oxo-DHEA		fluorine	carbamate	imidazole	BF4			
7-oxo-DHEA	phosphate ester		fluorine	carbamate	imidazole	BF4		
Acesulfame								
Acesulfame	phosphate ester		fluorine	carbamate	imidazole	BF4		
Acetohydroxamic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Acetohydroxamic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Acetohydroxamic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Adenine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Adenine	*sulfonic acid	*phosphoric acid	N-oxide	ester	ether	fluorine	acetate	thione
Adipic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Alanine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Alanine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Allopurinaol	phosphate ester		fluorine	carbamate	imidazole	BF4		
Allopurinaol	phosphate ester		fluorine	carbamate	imidazole	BF4		
Arginine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Arginine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Ascorbic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Ascorbic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Ascorbic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Asparagine	phosphate ester		fluorine	carbamate	imidazole	BF4		

TABLE II

Co-crystal Former					
1,5-Napthalene-disulfonic Acid					
1-Hydroxy-2-naphthoic acid					
1-Hydroxy-2-naphthoic acid					
4-Aminobenzoic Acid	N-SO2	thiourea	iodine		
4-Aminobenzoic Acid	N-SO2	thiourea	iodine		
4-aminopyridine	N-SO2	thiourea	iodine		
4-aminopyridine	dithiadiazocyclopentadienyl				
4-Chlorobenzene-Sulfonic Acid					
4-ethoxyphenyl Urea	N-SO2	thiourea	iodine	epoxide	peroxide
4-ethoxyphenyl Urea	N-SO2	thiourea	iodine		
7-oxo-DHEA					
7-oxo-DHEA	N-SO2	thiourea	iodine		
Acesulfame					
Acesulfame	N-SO2	thiourea	iodine	epoxide	peroxide
Acetohydroxamic Acid	N-SO2	thiourea	iodine	epoxide	peroxide
Acetohydroxamic Acid	N-SO2	thiourea	iodine		
Acetohydroxamic Acid	N-SO2	thiourea	iodine	epoxide	
Adenine	N-SO2	thiourea	iodine		
Adenine	dithiadiazocyclopentadienyl				
Adipic acid	N-SO2	thiourea	iodine		
Alanine	N-SO2	thiourea	iodine		
Alanine	N-SO2	thiourea	iodine		
Allopurinaol	N-SO2	thiourea	iodine	epoxide	
Allopurinaol	N-SO2	thiourea	iodine		
Arginine	N-SO2	thiourea	iodine		
Arginine	N-SO2	thiourea	iodine		
Ascorbic Acid	N-SO2	thiourea	iodine		
Ascorbic Acid	N-SO2	thiourea	iodine	epoxide	
Ascorbic Acid	N-SO2	thiourea	iodine		
Asparagine	N-SO2	thiourea	iodine		

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group					
Asparagine	Amide	alcohol	ketone	thiol	amide	amine	analine
Asparagine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Aspartic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine
Aspartic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Benzenesulfonic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide
Benzoic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Caffeine	Ketone	alcohol		thiol	amide	amine	analine
Camphoric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Capric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Genistein	Ketone	alcohol		thiol	amide	amine	analine
Genistein	Phenol	amine	amide	sulfoxide	n	pyridine	cyano
Genistein	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide
Cinnamic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Citric Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Citric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Clemizole	Pyrrolidine	*alcohol	pyridinium	*	*amide	nitro	*amine
Cyclamic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine
Cyclamic Acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide
Cysteine	Amine	alcohol	ketone	thiol	amide	amine	analine
Cysteine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Cysteine	Thiol	carboxylic acid	sodium	aldehyde	ketone	-N	cadmium
Dimethylglycine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Dimethylglycine	Amine	alcohol	ketone	thiol	amide	amine	analine
D-ribose	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide
D-ribose	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Fumaric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Galactaric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Galactaric acid	alcohol	alcohol	ketone	thiol	amide	amine	analine
Chrysin	Ketone	alcohol		thiol	amide	amine	analine
Chrysin	Phenol	amine	amide	sulfoxide	n	pyridine	cyano
Chrysin	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide

TABLE II

Co-crystal Former								
Asparagine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Asparagine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Aspartic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Aspartic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Benzenesulfonic Acid	Carboxylic Acid	amine	metals	thioether		sulfate	alcohol	
Benzoic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Caffeine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Camphoric acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Capric acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Genistein	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Genistein	aldehyde		alchohol		ester	ether	n-oxide	chlorine
Genistein	chlorate	chlorine		cyano	ester	amine	nitro	nitrate
Cinnamic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Citric Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Citric Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Clemizole	*carboxilic acid	*sulfonamide	*ketone	ether	triazole		ammonium	oxime
Cyclamic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Cyclamic Acid	Carboxylic Acid	amine	metals	thioether		sulfate	alcohol	
Cysteine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Cysteine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Cysteine		arsenic	chlorine	alcohol	potassium	Ru		Rb
Dimethylglycine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Dimethylglycine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
D-ribose	chlorate	chlorine		cyano	ester	amine	nitro	nitrate
D-ribose	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Fumaric Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Galactaric acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Galactaric acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals
Chrysin	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Chrysin	aldehyde		alchohol		ester	ether	n-oxide	chlorine
Chrysin	chlorate	chlorine		cyano	ester	amine	nitro	nitrate

TABLE II

Co-crystal Former								
Asparagine	metals	aldehyde	ester	ether	cyano		furan	bromine
Asparagine	metals	aldehyde	ester	ether	cyano		furan	bromine
Aspartic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Aspartic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Benzenesulfonic Acid								
Benzoic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Caffeine	metals	aldehyde	ester	ether	cyano		furan	bromine
Camphoric acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Capric acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Genistein	metals	aldehyde	ester	ether	cyano		furan	bromine
Genistein	fluorine	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid
Genistein	bromine	aldehyde	ketone	peroxide	epoxide			heterocyclic-S
Cinnamic acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Citric Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Citric Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Clemizole	*chlorine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone
Cyclamic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Cyclamic Acid								
Cysteine	metals	aldehyde	ester	ether	cyano		furan	bromine
Cysteine	metals	aldehyde	ester	ether	cyano		furan	bromine
Cysteine	Sb							
Dimethylglycine	metals	aldehyde	ester	ether	cyano		furan	bromine
Dimethylglycine	metals	aldehyde	ester	ether	cyano		furan	bromine
D-ribose	bromine	aldehyde	ketone	peroxide	epoxide			heterocyclic-S
D-ribose	metals	aldehyde	ester	ether	cyano		furan	bromine
Fumaric Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Galactaric acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Galactaric acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Chrysin	metals	aldehyde	ester	ether	cyano		furan	bromine
Chrysin	fluorine	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid
Chrysin	bromine	aldehyde	ketone	peroxide	epoxide			heterocyclic-S

TABLE II

Co-crystal Former						
Asparagine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Asparagine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Aspartic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Aspartic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Benzenesulfonic Acid						
Benzoic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Caffeine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Camphoric acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Capric acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Genistein	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Genistein	carboxylic acid	nitro	sulfone	analine		
Genistein	iodine	ester	ether	carboxylic acid	sulfate	sulfone
Cinnamic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Citric Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Citric Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Clemizole	thiocyanate	*bromine		hydroxamic acid	cyano	carboxamide
Cyclamic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Cyclamic Acid						
Cysteine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Cysteine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Cysteine						
Dimethylglycine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Dimethylglycine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
D-ribose	iodine	ester	ether	carboxylic acid	sulfate	sulfone
D-ribose	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Fumaric Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Galactaric acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Galactaric acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester
Chrysin	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Chrysin	carboxylic acid	nitro	sulfone	analine		
Chrysin	iodine	ester	ether	carboxylic acid	sulfate	sulfone

TABLE II

Co-crystal Former								
Asparagine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Asparagine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Aspartic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Aspartic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Benzenesulfonic Acid								
Benzoic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Caffeine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Camphoric acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Capric acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Genistein	phosphate ester		fluorine	carbamate	imidazole	BF4		
Genistein								
Genistein		alcohol		phospphate	cyanamide			
Cinnamic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Citric Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Citric Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Clemizole	*sulfonic acid	*phosphoric acid	N-oxide	ester	ether	fluorine	acetate	thione
Cyclamic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Cyclamic Acid								
Cysteine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Cysteine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Cysteine								
Dimethylglycine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Dimethylglycine	phosphate ester		fluorine	carbamate	imidazole	BF4		
D-ribose		alcohol		phospphate	cyanamide			
D-ribose	phosphate ester		fluorine	carbamate	imidazole	BF4		
Fumaric Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Galactaric acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Galactaric acid		fluorine	carbamate	imidazole	BF4			
Chrysin	phosphate ester		fluorine	carbamate	imidazole	BF4		
Chrysin								
Chrysin		alcohol		phospphate	cyanamide			

TABLE II

Co-crystal Former					
Asparagine	N-SO2	thiourea	iodine	epoxide	peroxide
Asparagine	N-SO2	thiourea	iodine		
Aspartic Acid	N-SO2	thiourea	iodine		
Aspartic Acid	N-SO2	thiourea	iodine		
Benzenesulfonic Acid					
Benzoic Acid	N-SO2	thiourea	iodine		
Caffeine	N-SO2	thiourea	iodine		
Camphoric acid	N-SO2	thiourea	iodine		
Capric acid	N-SO2	thiourea	iodine		
Genistein	N-SO2	thiourea	iodine		
Genistein					
Genistein					
Cinnamic acid	N-SO2	thiourea	iodine		
Citric Acid	N-SO2	thiourea	iodine	epoxide	
Citric Acid	N-SO2	thiourea	iodine		
Clemizole	dithiadiazocyclopentadienyl				
Cyclamic Acid	N-SO2	thiourea	iodine		
Cyclamic Acid					
Cysteine	N-SO2	thiourea	iodine		
Cysteine	N-SO2	thiourea	iodine		
Cysteine					
Dimethylglycine	N-SO2	thiourea	iodine		
Dimethylglycine	N-SO2	thiourea	iodine		
D-ribose					
D-ribose	N-SO2	thiourea	iodine	epoxide	
Fumaric Acid	N-SO2	thiourea	iodine		
Galactaric acid	N-SO2	thiourea	iodine		
Galactaric acid					
Chrysin	N-SO2	thiourea	iodine		
Chrysin					
Chrysin					

TABLE II

C -crystal Former	Co-crystal Former Functional Group	Interacting Group					
Gentisic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Gentisic acid	Phenol	amine	amide	sulfoxide	n	pyridine	cyano
Glucamine, N-methyl	alcohol	alcohol	ketone	thiol	amide	amine	analine
Glucamine, N-methyl	Amine	alcohol	ketone	thiol	amide	amine	analine
Gluconic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Gluconic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Glucosamine	alcohol	alcohol	ketone	thiol	amide	amine	analine
Glucuronic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Glucuronic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine
Glucuronic acid	Aldehyde	alcohol	ketone	thiol	amide	amine	analine
Glutamic Acid	Amine	alcohol	ketone	thiol	amide	amine	analine
Glutamic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Glutamine	Amine	alcohol	ketone	thiol	amide	amine	analine
Glutamine	Amide	alcohol	ketone	thiol	amide	amine	analine
Glutamine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Glutaric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Glycine	Amine	alcohol	ketone	thiol	amide	amine	analine
Glycine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Glycolic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Glycolic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Hippuric Acid	Amide	alcohol	ketone	thiol	amide	amine	analine
Hippuric Acid	Amine	alcohol	ketone	thiol	amide	amine	analine
Hippuric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Histidine	Amine	alcohol	ketone	thiol	amide	amine	analine
Histidine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Histidine	Imidazole	imidazole	chlorine	acetamide	carboxylate		thione
Hydroquinone	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Hydroquinone	Phenol	amine	amide	sulfoxide	n	pyridine	cyano
Imidazole	Amine	alcohol	ketone	thiol	amide	amine	analine
Ipriflavone	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide
Ipriflavone	Ketone	alcohol		thiol	amide	amine	analine
Isoleucine	Amine	alcohol	ketone	thiol	amide	amine	analine

TABLE II

Co-crystal Former								
Gentisic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Gentisic acid	aldehyde		alchohol		ester	ether	n-oxide	chlorine
Glucamine, N-methyl	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals
Glucamine, N-methyl	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Gluconic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Gluconic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Glucosamine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Glucuronic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Glucuronic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals
Glucuronic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid
Glutamic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Glutamic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Glutamine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Glutamine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Glutamine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Glutaric Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Glycine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Glycine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Glycolic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Glycolic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Hippuric Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Hippuric Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Hippuric Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Histidine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Histidine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Histidine	nitro	cyanamide	ketone	cyano	Carboxylic Acid	alcohol		thiol
Hydroquinone	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Hydroquinone	aldehyde		alchohol		ester	ether	n-oxide	chlorine
Imidazole	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Ipriflavone	chlorate	chlorine		cyano	ester	amine	nitro	nitrate
Ipriflavone	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Isoleucine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid

TABLE II

Co-crystal Former								
Gentisic acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Gentisic acid	fluorine	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid
Glucamine, N-methyl	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glucamine, N-methyl	metals	aldehyde	ester	ether	cyano		furan	bromine
Gluconic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Gluconic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Glucosamine	metals	aldehyde	ester	ether	cyano		furan	bromine
Glucuronic acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Glucuronic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Glucuronic acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Glutamic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Glutamic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Glutamine	metals	aldehyde	ester	ether	cyano		furan	bromine
Glutamine	metals	aldehyde	ester	ether	cyano		furan	bromine
Glutamine	metals	aldehyde	ester	ether	cyano		furan	bromine
Glutaric Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Glycine	metals	aldehyde	ester	ether	cyano		furan	bromine
Glycine	metals	aldehyde	ester	ether	cyano		furan	bromine
Glycolic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Glycolic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Hippuric Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Hippuric Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Hippuric Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Histidine	metals	aldehyde	ester	ether	cyano		furan	bromine
Histidine	metals	aldehyde	ester	ether	cyano		furan	bromine
Histidine	amine	phosphinic acid hemihydrate	chlorine	sulfonyl	sulfoxide	amide	fluorine	sulfonate ester
Hydroquinone	metals	aldehyde	ester	ether	cyano		furan	bromine
Hydroquinone	fluorine	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid
Imidazole	metals	aldehyde	ester	ether	cyano		furan	bromine
Ipriflavone	bromine	aldehyde	ketone	peroxide	epoxide			heterocyclic-S
Ipriflavone	metals	aldehyde	ester	ether	cyano		furan	bromine
Isoleucine	metals	aldehyde	ester	ether	cyano		furan	bromine

TABLE II

Co-crystal Former						
Gentisic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Gentisic acid	carboxylic acid	nitro	sulfone	analine		
Glucamine, N-methyl	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester
Glucamine, N-methyl	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Gluconic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Gluconic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glucosamine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glucuronic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glucuronic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester
Glucuronic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glutamic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glutamic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glutamine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glutamine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glutamine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glutaric Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glycine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glycine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glycolic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glycolic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Glycolic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Hippuric Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Hippuric Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Hippuric Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Histidine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Histidine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Histidine						
Hydroquinone	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Hydroquinone	carboxylic acid	nitro	sulfone	analine		
Imidazole	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Ipriflavone	iodine	ester	ether	carboxylic acid	sulfate	sulfone
Ipriflavone	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Isoleucine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone

TABLE II

Co-crystal Former								
Gentisic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Gentisic acid								
Glucamine, N-methyl		fluorine	carbamate	imidazole	BF4			
Glucamine, N-methyl	phosphate ester		fluorine	carbamate	imidazole	BF4		
Gluconic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Gluconic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glucosamine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glucuronic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glucuronic acid		fluorine	carbamate	imidazole	BF4			
Glucuronic acid	phosphate ester		fluorine	carbamate	imidazole	BF4	alkane	aromatic
Glutamic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glutamic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glutamine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glutamine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glutamine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glutaric Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glycine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glycine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glycine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glycolic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Glycolic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Hippuric Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Hippuric Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Hippuric Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Histidine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Histidine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Histidine								
Hydroquinone	phosphate ester		fluorine	carbamate	imidazole	BF4		
Hydroquinone								
Imidazole	phosphate ester		fluorine	carbamate	imidazole	BF4		
Ipriflavone		alcohol		phospphate	cyanamide			
Ipriflavone	phosphate ester		fluorine	carbamate	imidazole	BF4		
Isoleucine	phosphate ester		fluorine	carbamate	imidazole	BF4		

TABLE II

Co-crystal Former					
Gentisic acid	N-SO2	thiourea	iodine		
Gentisic acid					
Glucamine, N-methyl					
Glucamine, N-methyl	N-SO2	thiourea	iodine		
Gluconic Acid	N-SO2	thiourea	iodine	epoxide	
Gluconic Acid	N-SO2	thiourea	iodine		
Glucosamine	N-SO2	thiourea	iodine	epoxide	
Glucuronic acid	N-SO2	thiourea	iodine		
Glucuronic acid					
Glucuronic acid	N-SO2	thiourea	iodine	epoxide	
Glutamic Acid	N-SO2	thiourea	iodine		
Glutamic Acid	N-SO2	thiourea	iodine		
Glutamine	N-SO2	thiourea	iodine		
Glutamine	N-SO2	thiourea	iodine	epoxide	peroxide
Glutamine	N-SO2	thiourea	iodine		
Glutaric Acid	N-SO2	thiourea	iodine		
Glycine	N-SO2	thiourea	iodine		
Glycine	N-SO2	thiourea	iodine		
Glycolic Acid	N-SO2	thiourea	iodine	epoxide	
Glycolic Acid	N-SO2	thiourea	iodine		
Hippuric Acid	N-SO2	thiourea	iodine	epoxide	peroxide
Hippuric Acid	N-SO2	thiourea	iodine		
Hippuric Acid	N-SO2	thiourea	iodine		
Histidine	N-SO2	thiourea	iodine		
Histidine	N-SO2	thiourea	iodine		
Histidine					
Hydroquinone	N-SO2	thiourea	iodine	epoxide	
Hydroquinone					
Imidazole	N-SO2	thiourea	iodine		
Ipriflavone					
Ipriflavone	N-SO2	thiourea	iodine		
Isoleucine	N-SO2	thiourea	iodine		

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group					
Isoleucine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
lactobionic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Lactobionic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine
Lactobionic acid	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide
Lauric acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Leucine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Leucine	Amine	alcohol	ketone	thiol	amide	amine	analine
Lysine	Amine	alcohol	ketone	thiol	amide	amine	analine
Lysine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Maleic	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Malic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Malic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Malonic	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Mandelic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Mandelic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Methionine	Amine	alcohol	ketone	thiol	amide	amine	analine
Methionine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Methionine	Thioether	-N	amide	amine	_s	Sp2 amine	sulfoxide
Nicotinamide	Pyridine	*alcohol		*	*amide	nitro	*amine
Nicotinamide	Amide	alcohol	ketone	thiol	amide	amine	analine
Nicotinic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Nicotinic Acid	Pyridine	*alcohol		*	*amide	nitro	*amine
Orotic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Orotic acid	Lactam	alcohol	ketone	thiol	amide	amine	analine
Oxalic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Palmitic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Pamoic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Pamoic acid	alcohol	alcohol	ketone	thiol	amide	amine	analine
Pamoic acid	Phenol	amine	amide	sulfoxide	n	pyridine	cyano
Phenylalanine	Amine	alcohol	ketone	thiol	amide	amine	analine
Phenylalanine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Piperazine	Amine	alcohol	ketone	thiol	amide	amine	analine
Procaine	Amine	alcohol	ketone	thiol	amide	amine	analine

TABLE II

Co-crystal Former								
Isoleucine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
lactobionic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Lactobionic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals
Lactobionic acid	chlorate	chlorine		cyano	ester	amine	nitro	nitrate
Lauric acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Leucine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Leucine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Lysine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Lysine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Maleic	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Malic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Malic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Malonic	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Mandelic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Mandelic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Methionine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Methionine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Methionine	chlorate	chlorine		cyano	ester	amine	nitro	nitrate
Nicotinamide	*Carboxylic Acid	*sulfonamide	*ketone	ether	triazole		ammonium	oxime
Nicotinamide	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Nicotinic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Nicotinic Acid	*Carboxylic Acid	*sulfonamide	*ketone	ether	triazole		ammonium	oxime
Orotic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Orotic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Oxalic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Palmitic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Pamoic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Pamoic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals
Pamoic acid	aldehyde		alchohol		ester	ether	n-oxide	chlorine
Phenylalanine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Phenylalanine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Piperazine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Procaine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid

TABLE II

Co-crystal Former								
Isoleucine	metals	aldehyde	ester	ether	cyano		furan	bromine
lactobionic acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Lactobionic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Lactobionic acid	bromine	aldehyde	ketone	peroxide	epoxide			heterocyclic-S
Lauric acid		aldehyde	ester	ether	cyano		furan	bromine
Leucine	metals	aldehyde	ester	ether	cyano		furan	bromine
Leucine	metals	aldehyde	ester	ether	cyano		furan	bromine
Lysine	metals	aldehyde	ester	ether	cyano		furan	bromine
Lysine	metals	aldehyde	ester	ether	cyano		furan	bromine
Maleic	metals	aldehyde	ester	ether	cyano		furan	bromine
Malic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Malic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Malonic	metals	aldehyde	ester	ether	cyano		furan	bromine
Mandelic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Mandelic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Methionine	metals	aldehyde	ester	ether	cyano		furan	bromine
Methionine	metals	aldehyde	ester	ether	cyano		furan	bromine
Methionine	bromine	aldehyde	ketone	peroxide	epoxide	Ag	Se	heterocyclic-S
Nicotinamide	*chlorine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone
Nicotinamide	metals	aldehyde	ester	ether	cyano		furan	bromine
Nicotinic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Nicotinic Acid	*chlorine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone
Orotic acid		aldehyde	ester	ether	cyano		furan	bromine
Orotic acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Oxalic acid		aldehyde	ester	ether	cyano		furan	bromine
Palmitic acid		aldehyde	ester	ether	cyano		furan	bromine
Pamoic acid		aldehyde	ester	ether	cyano		furan	bromine
Pamoic acid	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Pamoic acid	fluorine	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid
Phenylalanine	metals	aldehyde	ester	ether	cyano		furan	bromine
Phenylalanine	metals	aldehyde	ester	ether	cyano		furan	bromine
Piperazine	metals	aldehyde	ester	ether	cyano		furan	bromine
Procaine	metals	aldehyde	ester	ether	cyano		furan	bromine

TABLE II

Co-crystal Former						
Isoleucine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
lactobionic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Lactobionic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester
Lactobionic acid	iodine	ester	ether	carboxylic acid	sulfate	sulfone
Lauric acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Leucine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Leucine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Lysine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Lysine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Maleic	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Malic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Malic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Malonic	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Mandelic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Mandelic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Methionine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Methionine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Methionine	iodine	ester	ether	carboxylic acid	sulfate	sulfone
Nicotinamide	thiocyanate	*bromine		hydroxamic acid	cyano	carboxamide
Nicotinamide	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Nicotinic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Nicotinic Acid	thiocyanate	*bromine		hydroxamic acid	cyano	carboxamide
Orotic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Orotic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Oxalic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Palmitic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Pamoic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Pamoic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester
Pamoic acid	carboxylic acid	nitro	sulfone	analine		
Phenylalanine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Phenylalanine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Piperazine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Procaine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone

TABLE II

Co-crystal Former								
Isoleucine	phosphate ester		fluorine	carbamate	imidazole	BF4		
lactobionic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Lactobionic acid		fluorine	carbamate	imidazole	BF4			
Lactobionic acid		alcohol		phospphate	cyanamide			
Lauric acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Leucine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Leucine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Lysine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Lysine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Maleic	phosphate ester		fluorine	carbamate	imidazole	BF4		
Malic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Malic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Malonic	phosphate ester		fluorine	carbamate	imidazole	BF4		
Mandelic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Mandelic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Methionine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Methionine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Methionine		alcohol		phospphate				
Nicotinamide	*sulfonic acid	*phosphoric acid	N-oxide	ester	ether	fluorine	acetate	thione
Nicotinamide	phosphate ester		fluorine	carbamate	imidazole	BF4		
Nicotinic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Nicotinic Acid	*sulfonic acid	*phosphoric acid	N-oxide	ester	ether	fluorine	acetate	thione
Orotic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Orotic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Oxalic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Palmitic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Pamoic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Pamoic acid		fluorine	carbamate	imidazole	BF4			
Pamoic acid								
Phenylalanine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Phenylalanine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Piperazine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Procaine	phosphate ester		fluorine	carbamate	imidazole	BF4		

TABLE II

Co-crystal Former					
Isoleucine	N-SO2	thiourea	iodine		
lactobionic acid	N-SO2	thiourea	iodine		
Lactobionic acid					
Lactobionic acid					
Lauric acid	N-SO2	thiourea	iodine		
Leucine	N-SO2	thiourea	iodine		
Leucine	N-SO2	thiourea	iodine		
Lysine	N-SO2	thiourea	iodine		
Lysine	N-SO2	thiourea	iodine		
Maleic	N-SO2	thiourea	iodine		
Malic Acid	N-SO2	thiourea	iodine	epoxide	
Malic Acid	N-SO2	thiourea	iodine		
Malonic	N-SO2	thiourea	iodine		
Mandelic Acid	N-SO2	thiourea	iodine	epoxide	
Mandelic Acid	N-SO2	thiourea	iodine		
Methionine	N-SO2	thiourea	iodine		
Methionine	N-SO2	thiourea	iodine		
Methionine					
Nicotinamide	dithiadiazocyclopentadienyl				
Nicotinamide	N-SO2	thiourea	iodine	epoxide	peroxide
Nicotinic Acid	N-SO2	thiourea	iodine		
Nicotinic Acid	dithiadiazocyclopentadienyl				
Orotic acid	N-SO2	thiourea	iodine		
Orotic acid	N-SO2	thiourea	iodine	epoxide	peroxide
Oxalic acid	N-SO2	thiourea	iodine		
Palmitic acid	N-SO2	thiourea	iodine		
Pamoic acid	N-SO2	thiourea	iodine		
Pamoic acid					
Pamoic acid					
Phenylalanine	N-SO2	thiourea	iodine		
Phenylalanine	N-SO2	thiourea	iodine		
Piperazine	N-SO2	thiourea	iodine		
Procaine	N-SO2	thiourea	iodine		

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group					
Procaine	Ketone	alcohol		thiol	amide	amine	analine
Proline	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Proline	Amine	alcohol	ketone	thiol	amide	amine	analine
p-Toluenesulfonic acid	Sulfonic Acid	pyridine	ketone	aldehyde	ether	ester	amide
Pyridoxamine	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Pyridoxamine	Amine	alcohol	ketone	thiol	amide	amine	analine
Pyridoxamine	Pyridine	*alcohol		*	*amide	nitro	*amine
Pyridoxine (4-Pyridoxic Acid)	Pyridine	*alcohol	pyridinium	*	*amide	nitro	*amine
Pyridoxine (4-Pyridoxic Acid)	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Pyroglutamic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Pyroglutamic acid	Lactam	alcohol	ketone	thiol	amide	amine	analine
Quercetin	Ketone	alcohol		thiol	amide	amine	analine
Quercetin	Phenol	amine	amide	sulfoxide	n	pyridine	cyano
Quercetin	Ether	aromatic-N	amide	amine	aromatic_s	Sp2 amine	sulfoxide
Resveratrol	Ketone	alcohol		thiol	amide	amine	analine
Resveratrol	Phenol	amine	amide	sulfoxide	n	pyridine	cyano
Saccharin	Amide	alcohol	ketone	thiol	amide	amine	analine
Saccharin	Ketone	alcohol		thiol	amide	amine	analine
Saccharin	Sulfoxide	pyridine	ketone	aldehyde	ether	ester	amide
Saccharin	Amine	alcohol	ketone	thiol	amide		analine
Salicylic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Salicylic Acid	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Salicylic Acid, 4-amino	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Salicylic Acid, 4-amino	alcohol	alcohol	ketone	thiol	amide	amine	analine
Salicylic Acid, 4-amino	Amine	alcohol	ketone	thiol	amide	amine	analine
Sebacic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Serine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Serine	Amine	alcohol	ketone	thiol	amide	amine	analine
Serine	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Stearic acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine

TABLE II

Co-crystal Former								
Procaine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Proline	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Proline	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
p-Toluenesulfonic acid	Carboxylic Acid	amine	metals	thioether		sulfate	alcohol	
Pyridoxamine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Pyridoxamine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Pyridoxamine	*Carboxylic Acid	*sulfonamide	*ketone	ether	triazole		ammonium	oxime
Pyridoxine (4-Pyridoxic Acid)	*Carboxylic Acid	*sulfonamide	*ketone	ether	triazole		ammonium	oxime
Pyridoxine (4-Pyridoxic Acid)	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Pyroglutamic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Pyroglutamic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Quercetin	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Quercetin	aldehyde		alchohol		ester	ether	n-oxide	chlorine
Quercetin	chlorate	chlorine		cyano	ester	amine	nitro	nitrate
Resveratrol	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Resveratrol	aldehyde		alchohol		ester	ether	n-oxide	chlorine
Resveratrol	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Saccharin	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Saccharin	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Saccharin	Carboxylic Acid	amine	metals	thioether		sulfate	alcohol	
Saccharin	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Salicylic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Salicylic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Salicylic Acid, 4-amino	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Salicylic Acid, 4-amino	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	carboxilic acid	metals
Salicylic Acid, 4-amino	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Sebacic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Serine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Serine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Serine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Stearic acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid

TABLE II

Co-crystal Former								
Procaine	metals	aldehyde	ester	ether	cyano		furan	bromine
Proline	metals	aldehyde	ester	ether	cyano		furan	bromine
Proline	metals	aldehyde	ester	ether	cyano		furan	bromine
p-Toluenesulfonic acid								
Pyridoxamine	metals	aldehyde	ester	ether	cyano		furan	bromine
Pyridoxamine	metals	aldehyde	ester	ether	cyano		furan	bromine
Pyridoxamine	*chlorine		thiol	n-heterocyclic ring	thionedisulfide		iodine	hydrazone
Pyridoxine (4-Pyridoxic Acid)	*chlorine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone
Pyridoxine (4-Pyridoxic Acid)	metals	aldehyde	ester	ether	cyano		furan	bromine
Pyroglutamic acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Pyroglutamic acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Quercetin	metals	aldehyde	ester	ether	cyano		furan	bromine
Quercetin	fluorine	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid
Quercetin	bromine	aldehyde	ketone	peroxide	epoxide			heterocyclic-S
Resveratrol	metals	aldehyde	ester	ether	cyano		furan	bromine
Resveratrol	fluorine	bromine	iodine	ketone	sulfonic acid	sulfate	phosphate	phosphonic acid
Saccharin	metals	aldehyde	ester	ether	cyano		furan	bromine
Saccharin	metals	aldehyde	ester	ether	cyano		furan	bromine
Saccharin								
Saccharin	metals	aldehyde	ester	ether	cyano		furan	bromine
Salicylic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Salicylic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Salicylic Acid, 4-amino	metals	aldehyde	ester	ether	cyano		furan	bromine
Salicylic Acid, 4-amino	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Salicylic Acid, 4-amino	metals	aldehyde	ester	ether	cyano		furan	bromine
Sebacic acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Serine	metals	aldehyde	ester	ether	cyano		furan	bromine
Serine	metals	aldehyde	ester	ether	cyano		furan	bromine
Serine	metals	aldehyde	ester	ether	cyano		furan	bromine
Stearic acid	metals	aldehyde	ester	ether	cyano		furan	bromine

TABLE II

Co-crystal Former						
Procaine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Proline	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Proline	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
p-Toluenesulfonic acid						
Pyridoxamine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Pyridoxamine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Pyridoxamine	thiocyanate	*bromine		hydroxamic acid	cyano	carboxamide
Pyridoxine (4-Pyridoxic Acid)	thiocyanate	*bromine		hydroxamic acid	cyano	carboxamide
Pyridoxine (4-Pyridoxic Acid)	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Pyroglutamic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Pyroglutamic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Quercetin	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Quercetin	carboxylic acid	nitro	sulfone	analine		
Quercetin	iodine	ester	ether	carboxylic acid	sulfate	sulfone
Resveratrol	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Resveratrol	carboxylic acid	nitro	sulfone	analine		
Saccharin	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Saccharin	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Saccharin						
Saccharin	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Salicylic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Salicylic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Salicylic Acid, 4-amino	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Salicylic Acid, 4-amino	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester
Salicylic Acid, 4-amino	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Sebacic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Serine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Serine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Serine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Stearic acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone

TABLE II

Co-crystal Former								
Procaine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Proline	phosphate ester		fluorine	carbamate	imidazole	BF4		
Proline	phosphate ester		fluorine	carbamate	imidazole	BF4		
p-Toluenesulfonic acid								
Pyridoxamine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Pyridoxamine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Pyridoxamine	*sulfonic acid	*phosphoric acid	N-oxide	ester	ether	fluorine	acetate	thione
Pyridoxine (4-Pyridoxic Acid)	*sulfonic acid	*phosphoric acid	N-oxide	ester	ether	fluorine	acetate	thione
Pyridoxine (4-Pyridoxic Acid)	phosphate ester		fluorine	carbamate	imidazole	BF4		
Pyroglutamic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Pyroglutamic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Quercetin	phosphate ester		fluorine	carbamate	imidazole	BF4		
Quercetin								
Quercetin		alcohol		phospphate	cyanamide			
Resveratrol	phosphate ester		fluorine	carbamate	imidazole	BF4		
Resveratrol								
Saccharin	phosphate ester		fluorine	carbamate	imidazole	BF4		
Saccharin	phosphate ester		fluorine	carbamate	imidazole	BF4		
Saccharin								
Saccharin	phosphate ester		fluorine	carbamate	imidazole	BF4		
Salicylic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Salicylic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Salicylic Acid, 4-amino	phosphate ester		fluorine	carbamate	imidazole	BF4		
Salicylic Acid, 4-amino		fluorine	carbamate	imidazole	BF4			
Salicylic Acid, 4-amino	phosphate ester		fluorine	carbamate	imidazole	BF4		
Sebacic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Serine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Serine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Serine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Stearic acid	phosphate ester		fluorine	carbamate	imidazole	BF4		

TABLE II

Co-crystal Former					
Procaine	N-SO2	thiourea	iodine		
Proline	N-SO2	thiourea	iodine		
Proline	N-SO2	thiourea	iodine		
p-Toluenesulfonic acid					
Pyridoxamine	N-SO2	thiourea	iodine	epoxide	
Pyridoxamine	N-SO2	thiourea	iodine		
Pyridoxamine	dithiadiazocyclopentadienyl				
Pyridoxine (4-Pyridoxic Acid)	dithiadiazocyclopentadienyl				
Pyridoxine (4-Pyridoxic Acid)	N-SO2	thiourea	iodine	epoxide	
Pyroglutamic acid	N-SO2	thiourea	iodine		
Pyroglutamic acid	N-SO2	thiourea	iodine	epoxide	peroxide
Quercetin	N-SO2	thiourea	iodine		
Quercetin					
Quercetin					
Resveratrol	N-SO2	thiourea	iodine		
Resveratrol					
Saccharin	N-SO2	thiourea	iodine	epoxide	peroxide
Saccharin	N-SO2	thiourea	iodine		
Saccharin					
Saccharin	N-SO2	thiourea	iodine		
Salicylic Acid	N-SO2	thiourea	iodine		
Salicylic Acid	N-SO2	thiourea	iodine	epoxide	
Salicylic Acid, 4-amino	N-SO2	thiourea	iodine		
Salicylic Acid, 4-amino					
Salicylic Acid, 4-amino	N-SO2	thiourea	iodine		
Sebacic acid	N-SO2	thiourea	iodine		
Serine	N-SO2	thiourea	iodine		
Serine	N-SO2	thiourea	iodine		
Serine	N-SO2	thiourea	iodine	epoxide	
Stearic acid	N-SO2	thiourea	iodine		

TABLE II

Co-crystal Former	Co-crystal Former Functional Group	Interacting Group					
Succinic Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Tartaric Acid	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Threonine	Amine	alcohol	ketone	thiol	amide	amine	analine
Threonine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Threonine	alcohol	alcohol	ketone	thiol	amide	amine	analine
Tris	Amine	alcohol	ketone	thiol	amide	amine	analine
Tris	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Tryptophan	Amine	alcohol	ketone	thiol	amide	amine	analine
Tryptophan	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Tryptophan	Indole	*alcohol	pyridinium	*	*amide	nitro	*amine
Tyrosine	Amine	alcohol	ketone	thiol	amide	amine	analine
Tyrosine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Tyrosine	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Urea	Ketone	alcohol		thiol	amide	amine	analine
Urea	Amine	alcohol	ketone	thiol	amide	amine	analine
Urea	Amide	alcohol	ketone	thiol	amide	amine	analine
Valine	Amine	alcohol	ketone	thiol	amide	amine	analine
Valine	Carboxylic Acid	alcohol	ketone	thiol	amide	amine	analine
Vitamin K5	Amine	alcohol	ketone	thiol	amide	amine	analine
Vitamin K5	Alcohol	alcohol	ketone	thiol	amide	amine	analine
Xylitol	Alcohol	alcohol	ketone	thiol	amide	amine	analine

TABLE II

Co-crystal Former								
Succinic Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Tartaric Acid	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Threonine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Threonine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Threonine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Tris	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Tris	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Tryptophan	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Tryptophan	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Tryptophan	*carboxilic acid	*sulfonamide	*ketone	ether	triazole		ammonium	oxime
Tyrosine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Tyrosine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Tyrosine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Urea	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Urea	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Urea	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Valine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Valine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Valine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Vitamin K5	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		carboxilic acid
Vitamin K5	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid
Xylitol	phenol	phosphate	sulfate	sulfone	nitrate	pyridine		Carboxylic Acid

TABLE II

Co-crystal Former								
Succinic Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Tartaric Acid	metals	aldehyde	ester	ether	cyano		furan	bromine
Threonine	metals	aldehyde	ester	ether	cyano		furan	bromine
Threonine	metals	aldehyde	ester	ether	cyano		furan	bromine
Threonine	metals	aldehyde	ester	ether	cyano		furan	bromine
Tris	metals	aldehyde	ester	ether	cyano		furan	bromine
Tris	metals	aldehyde	ester	ether	cyano		furan	bromine
Tryptophan	metals	aldehyde	ester	ether	cyano		furan	bromine
Tryptophan	metals	aldehyde	ester	ether	cyano		furan	bromine
Tryptophan	*chlorine		thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone
Tyrosine	metals	aldehyde	ester	ether	cyano		furan	bromine
Tyrosine	metals	aldehyde	ester	ether	cyano		furan	bromine
Tyrosine	metals	aldehyde	ester	ether	cyano		furan	bromine
Urea	metals	aldehyde	ester	ether	cyano		furan	bromine
Urea	metals	aldehyde	ester	ether	cyano		furan	bromine
Urea	metals	aldehyde	ester	ether	cyano		furan	bromine
Valine	metals	aldehyde	ester	ether	cyano		furan	bromine
Valine	metals	aldehyde	ester	ether	cyano		furan	bromine
Vitamin K5	metals	aldehyde	ester	ether	cyano		furan	bromine
Vitamin K5	metals	aldehyde	ester	ether	cyano		furan	bromine
Vitamin K5	metals	aldehyde	ester	ether	cyano		furan	bromine
Xylitol	metals	aldehyde	ester	ether	cyano		furan	bromine

TABLE II

Co-crystal Former						
Succinic Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Tartaric Acid	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Threonine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Threonine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Threonine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Tris	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Tris	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Tryptophan	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Tryptophan	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Tryptophan	thiocyanate	*bromine		hydroxamic acid	cyano	carboxamide
Tyrosine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Tyrosine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Tyrosine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Urea	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Urea	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Urea	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Valine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Valine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Valine	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Vitamin K5	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Vitamin K5	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone
Xylitol	chlorine	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone

TABLE II

Co-crystal Former								
Succinic Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Tartaric Acid	phosphate ester		fluorine	carbamate	imidazole	BF4		
Threonine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Threonine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Threonine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Tris	phosphate ester		fluorine	carbamate	imidazole	BF4		
Tris	phosphate ester		fluorine	carbamate	imidazole	BF4		
Tryptophan	phosphate ester		fluorine	carbamate	imidazole	BF4		
Tryptophan	phosphate ester		fluorine	carbamate	imidazole	BF4		
Tryptophan	*sulfonic acid	*phosphoric acid	N-oxide	ester	ether	fluorine	acetate	thione
Tyrosine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Tyrosine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Tyrosine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Urea	phosphate ester		fluorine	carbamate	imidazole	BF4		
Urea	phosphate ester		fluorine	carbamate	imidazole	BF4		
Urea	phosphate ester		fluorine	carbamate	imidazole	BF4		
Valine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Valine	phosphate ester		fluorine	carbamate	imidazole	BF4		
Vitamin K5	phosphate ester		fluorine	carbamate	imidazole	BF4		
Vitamin K5	phosphate ester		fluorine	carbamate	imidazole	BF4		
Vitamin K5	phosphate ester		fluorine	carbamate	imidazole	BF4		
Xylitol	phosphate ester		fluorine	carbamate	imidazole	BF4		

TABLE II

Co-crystal Former					
Succinic Acid	N-SO2	thiourea	iodine		
Tartaric Acid	N-SO2	thiourea	iodine		
Threonine	N-SO2	thiourea	iodine		
Threonine	N-SO2	thiourea	iodine		
Threonine	N-SO2	thiourea	iodine	epoxide	
Tris	N-SO2	thiourea	iodine		
Tris	N-SO2	thiourea	iodine	epoxide	
Tryptophan	N-SO2	thiourea	iodine		
Tryptophan	N-SO2	thiourea	iodine		
Tryptophan	dithiadiazocyclopentadienyl				
Tyrosine	N-SO2	thiourea	iodine		
Tyrosine	N-SO2	thiourea	iodine		
Tyrosine	N-SO2	thiourea	iodine	epoxide	
Urea	N-SO2	thiourea	iodine		
Urea	N-SO2	thiourea	iodine		
Urea	N-SO2	thiourea	iodine	epoxide	peroxide
Valine	N-SO2	thiourea	iodine		
Valine	N-SO2	thiourea	iodine		
Vitamin K5	N-SO2	thiourea	iodine		
Vitamin K5	N-SO2	thiourea	iodine	epoxide	
Vitamin K5	N-SO2	thiourea	iodine	epoxide	
Xylitol	N-SO2	thiourea	iodine	epoxide	

TABLE III

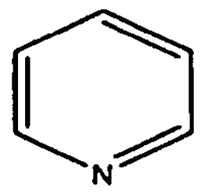
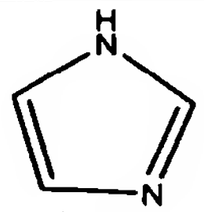
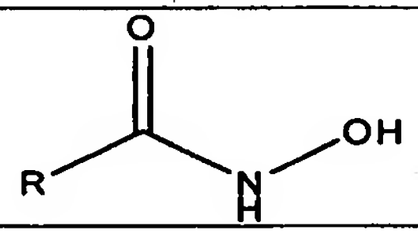
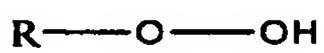
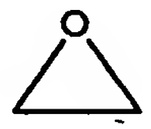
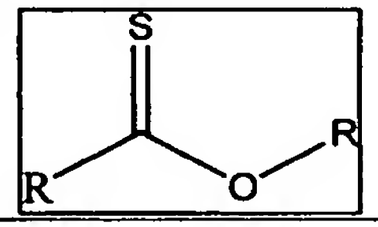
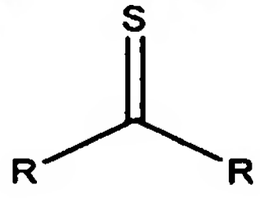
Functional Group	Functional Group Structure	Interacting Group				
pyridine		*alcohol	pyridinium	*amide	nitro	*amine
imidazole		imidazole	chlorine	acetamide	carboxylate	thione
Hydroxamic acid		hydroxamic acid	alcohol	phosphinic ester	alkane	pyridine
peroxide		ester	peroxide	amide	ether	alkane
epoxide		alkane	bromine	alcohol	ester	epoxide
thioester		aromatic	thioester	alkane	sulfamide	hydroxy
thioketone		alkane	thioketone	ketone	SULFAMIDE	AMINE

TABLE III

Functional Group									
pyridine	*carboxilic acid	*sulfonamide	*ketone	ether	triazole	alkane	ammonium	oxime	*chlorine
imidazole	nitro	cyanamide	ketone	cyano	carboxilic acid	alcohol	alkane	thiol	amine
Hydroxamic acid	amide	sulfonamide	carboxylate	phosphine	amine	aromatic			
peroxide	N-heterocycle	aromatic	alcohol	pyrimidinedione	analine	thiazole	peroxy acid	ketone	carboxilic acid
epoxide	amide	alkene	hydrazone	aromatic	thioether	ketone	aldehyde	chlorine	carboxilic acid
thioester	bromine	iodine	amine	cyano	thioketone	amide		chlorine	nitro
thioketone	thiol	sulfoxide	oxo	chlorine	bromine	AROMATIC	alkene	sulfone	iodine

TABLE III

Functional Group									
pyridine	alkyne	thiol	n-heterocyclic ring	thionedisulfide	pyrrolidindione	iodine	hydrazone	thiocyanate	*bromine
imidazole	phosphinic acid hemihydrate	chlorine	sulfonyl	sulfoxide	amide	fluorine	sulfonate ester		
Hydroxamic acid									
peroxide	azide	phosphine oxide	sulfonamide	analine					
epoxide	alkyne		ammonium	fluorine	nitro	amine	cyano		
thioester									
thioketone	AZOXY	potassium	epoxide	n-oxide	cyano	iron	cobalt	amine	sulfate

TABLE III

Functional Group										
pyridine	aromatic	hydroxamic acid	cyano	carboxamide	*sulfonic acid	*phosphoric acid	N-oxide	ester	ether	fluorine
imidazole										
Hydroxamic acid										
peroxide										
epoxide										
thioester										
thioketone										

TABLE III

Functional Group								
pyridine	acetate	thione	dithiadiazocyclopentadienyl					
imidazole								
Hydroxamic acid								
peroxide								
epoxide								
thioester								
thioketone								

TABLE III

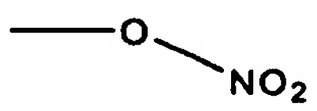
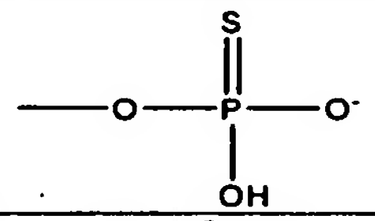
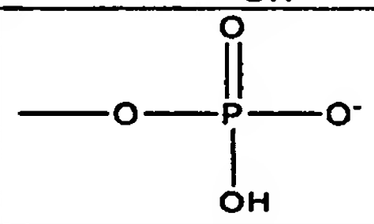
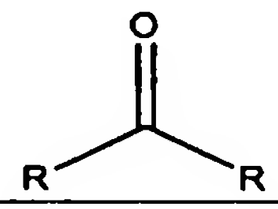
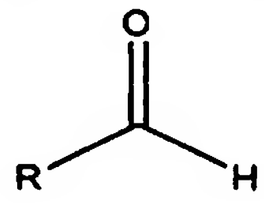
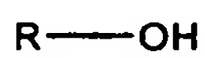
Functional Group	Functional Group Structure	Interacting Group				
nitrate ester		aromatic	amide	alkane	chlorine	nitrate ester
Thiophosphate ester-O		amine	imidazole	cyclic amide		
Phosphate ester		aromatic	alcohol	phosphate ester	aromatic N-ring	pyridine
Ketone		alcohol	ketone	thiol	amide	amine
Aldehyde		alcohol	ketone	thiol	amide	amine
Thiol		carboxylic acid	sodium	aldehyde	ketone	aromatic-N
Alcohol		alcohol	ketone	thiol	amide	amine

TABLE III

Functional Group									
nitrate ester	bromine	alcohol	ether	acetate					
Thiophosphate ester-O									
Phosphate ester	analine	amine		sodium	potassium	lithium	carboxylic acid	amide	alkane
Ketone	analine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid
Aldehyde	analine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid
Thiol	cadmium	alkane	arsenic	chlorine	alcohol	potassium	Ru	aromatic	Rb
Alcohol	analine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid

TABLE III

Functional Group									
nitrate ester									
Thiophosphate ester-O									
Phosphate ester									
Ketone	metals	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Aldehyde	metals	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Thiol	Sb								
Alcohol	metals	aldehyde	ester	ether	cyano		furan	bromine	chlorine

TABLE III

Functional Group										
nitrate ester										
Thiophosphate ester-O										
Phosphate ester										
Ketone	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole
Aldehyde	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole
Thiol										
Alcohol	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole

TABLE III

Functional Group								
nitrate ester								
Thiophosphate ester-O								
Phosphate ester								
Ketone	BF4	alkane	aromatic	N-SO2	thiourea	iodine		
Aldehyde	BF4	alkane	aromatic	N-SO2	thiourea	iodine	epoxide	
Thiol								
Alcohol	BF4	alkane	aromatic	N-SO2	thiourea	iodine	epoxide	

TABLE III

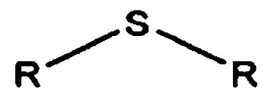
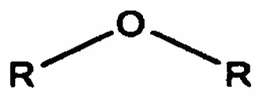
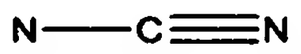
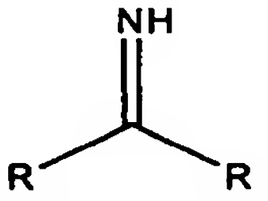
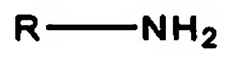
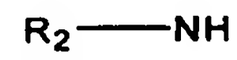
Functional Group	Functional Group Structure	Interacting Group				
Thioether		aromatic-N	amide	amine	aromatic_s	Sp2 amine
Ether		aromatic-N	amide	amine	aromatic_s	Sp2 amine
Cyanamide		cyano	amine	potassium	aromatic-N	bromine
Thiocyanate		aromatic-S	ester	ether		
sP2 amine		thioether	ether	metals	MoOCl4	BF4
Amine primary		alcohol	ketone	thiol	amide	amine
Amine secondary		alcohol	ketone	thiol	amide	amine

TABLE III

Functional Group									
Thioether	sulfoxide	chlorate	chlorine	alkyne	cyano	ester	amine	nitro	nitrate
Ether	sulfoxide	chlorate	chlorine	alkyne	cyano	ester	amine	nitro	nitrate
Cyanamide	sodium	imidazole	ether	n-heterocyclic	alcohol	cesium	Ag		
Thiocyanate									
sP2 amine	bromine	chlorine		Sp2 amine	sulfate	Osmium			
Amine primary	analine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid
Amine secondary	analine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid

TABLE III

Functional Group									
Thioether	bromine	aldehyde	ketone	peroxide	epoxide	Ag	Se	heterocyclic-S	iodine
Ether	bromine	aldehyde	ketone	peroxide	epoxide	Ag	Se	heterocyclic-S	iodine
Cyanamide									
Thiocyanate									
sP2 amine									
Amine primary	metals	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Amine secondary	metals	aldehyde	ester	ether	cyano		furan	bromine	chlorine

TABLE III

Functional Group										
Thioether	ester	ether	carboxylic acid	sulfate	sulfone	alkane	alcohol		phospphate	
Ether	ester	ether	carboxylic acid	sulfate	sulfone	alkane	alcohol		phospphate	cyanamide
Cyanamide										
Thiocyanate										
sP2 amine										
Amine primary	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole
Amine secondary	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole

TABLE III

Functional Group								
Thioether								
Ether								
Cyanamide								
Thiocyanate								
sP2 amine								
Amine primary	BF4	alkane	aromatic	N-SO2	thiourea	iodine		
Amine secondary	BF4	alkane	aromatic	N-SO2	thiourea	iodine		

TABLE III

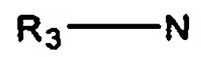
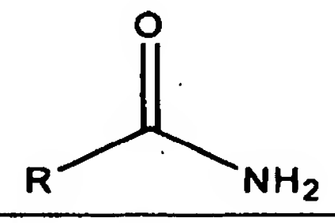
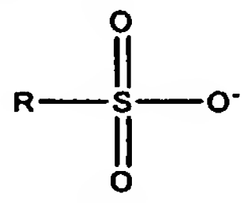
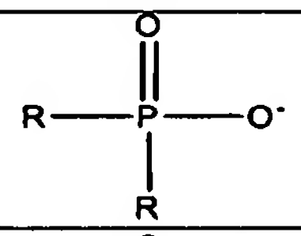
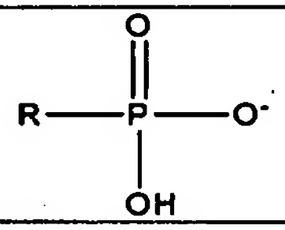
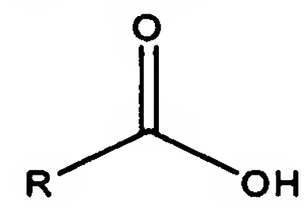
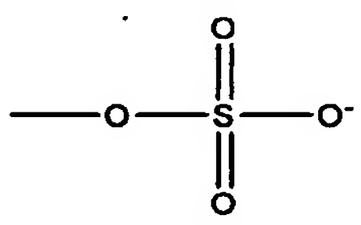
Functional Group	Functional Group Structure	Interacting Group				
Amine tertiary		alcohol	ketone	thiol	amide	amine
Amide		alcohol	ketone	thiol	amide	amine
Sulfonic acid		pyridine	ketone	aldehyde	ether	ester
Phosphinic acid		alkane	potassium	lithium	n-heterocyclic	oxime
Phosphonic acid		alkane	potassium	lithium	n-heterocyclic	oxime
Carboxylic acid		alcohol	ketone	thiol	amide	amine
Sulfate ester		pyridine	ketone	aldehyde	ether	ester

TABLE III

Functional Group									
Amine tertiary	analine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid
Amide	analine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid
Sulfonic acid	amide	carboxilic acid	amine	metals	thioether		sulfate	alcohol	
Phosphinic acid	amide	phenol	aromatic	amine	alcohol		metals		
Phosphonic acid	amide	phenol	aromatic	amine	alcohol		metals	carboxylic acid	Sp2 amine
Carboxylic acid	analine	phenol	phosphate	sulfate	sulfone	nitrate	pyridine	aromatic	carboxilic acid
Sulfate ester	amide	carboxilic acid	amine	metals	thioether	sulfate	alcohol		

TABLE III

Functional Group									
Amine tertiary	metals	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Amide	metals	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Sulfonic acid									
Phosphinic acid									
Phosphonic acid	analine	ether	phosphonic acid	aromatic-N	ketone	aldehyde	imidazole		
Carboxylic acid	metals	aldehyde	ester	ether	cyano		furan	bromine	chlorine
Sulfate ester									

TABLE III

Functional Group										
Amine tertiary	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole
Amide	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole
Sulfonic acid										
Phosphinic acid										
Phosphonic acid										
Carboxylic acid	s-heterocyclic	pyridine	cyano	n-heterocyclic	ketone	phosphate ester		fluorine	carbamate	imidazole
Sulfate ester										

TABLE III

Functional Group								
Amine tertiary	BF4	alkane	aromatic	N-SO2	thiourea	iodine		
Amide	BF4	alkane	aromatic	N-SO2	thiourea	iodine	epoxide	peroxide
Sulfonic acid								
Phosphinic acid								
Phosphonic acid								
Carboxylic acid	BF4	alkane	aromatic	N-SO2	thiourea	iodine		
Sulfate ester								

TABLE III

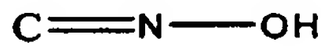
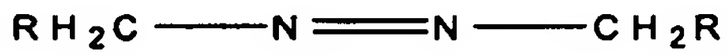
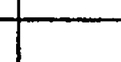
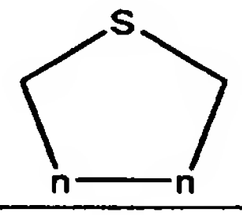
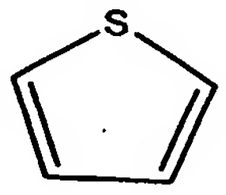
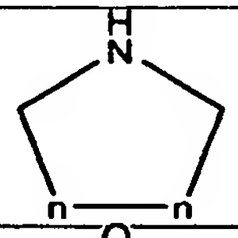
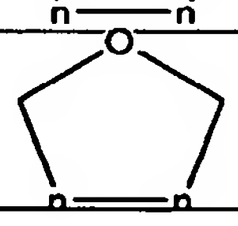
Functional Group	Functional Group Structure	Interacting Group				
Oxime		alcohol	alkane	amine	amide	ether
Nitrile		metal	ketone	phenol	alcohol	
Diazo		Oxime				
Nitro		pyridine	ketone	aldehyde	ether	ester
S-heterocyclic ring		alcohol	thioketone	thioether	s-heterocyclic	ketone
Thiophene		chlorine	fluorine	amide	ketone	NO
N-heterocyclic ring		alcohol	thioketone	thioether	s-heterocyclic	ketone
O-heterocyclic ring		alcohol	thioketone	thioether	s-heterocyclic	ketone

TABLE III

Functional Group									
Oxime	ester	pyridine	n-aromatic	chlorate	chlorine	Sp2-N	diazo	thioketone	cyano
Nitrile	cyano	amine	analine	bromine	amide	alkane	carboxylic acid	chlorine	n-heterocyclic
Diazo									
Nitro	amide	carboxilic acid	amine	metals	thioether	sulfate	alcohol		
S-heterocyclic ring	aromatic	alkene	amine	chlorine	BF4	sulfate	ester	NO	ether
Thiophene	SO	CO							
N-heterocyclic ring	aromatic	alkene	amine	chlorine	BF4	sulfate	ester	NO	ether
O-heterocyclic ring	aromatic	alkene	amine	chlorine	BF4	sulfate	ester	NO	ether

TABLE III

Functional Group									
Oxime	n-oxide	ketone	aldehyde	carboxylic acid	bromine	aromatic	pyridine	BF4	
Nitrile	aromatic	potassium	aldehyde	thioether	pyridine	n-aromatic	bromine	ether	s-aromatic
Diazo									
Nitro									
S-heterocyclic ring	amide	iodine	carboxylic acid	sodium	cyano	chloride	furan		
Thiophene									
N-heterocyclic ring	amide	iodine	carboxylic acid	sodium	cyano	chloride	aldehyde		
O-heterocyclic ring	amide	iodine	carboxylic acid	sodium	cyano	chloride	aldehyde		

TABLE III

Functional Group										
Oxime										
Nitrile	thiophene									
Diazo										
Nitro										
S-heterocyclic ring										
Thiophene										
N-heterocyclic ring										
O-heterocyclic ring										

TABLE III

Functional Group								
Oxime								
Nitrile								
Diazo								
Nitro								
S-heterocyclic ring								
Thiophene								
N-heterocyclic ring								
O-heterocyclic ring								

TABLE III

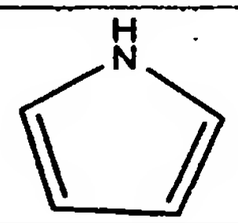
Functional Group	Functional Group Structure	Interacting Group				
Pyrrole		chlorine	fluorine	amide	ketone	NO
Furan		s-heterocyclic				

TABLE III

Functional Group									
Pyrrole	SO	CO	imidazole	pyridine	n-aromatic	aldehyde	carboxylic acid	sulfate	chlorine
Furan									

TABLE III

Functional Group									
Pyrrole	bromine	oxime	alcohol	phenol	ester	ether			
Furan									

TABLE III

Functional Group										
Pyrrole										
Furan										

TABLE III

Functional Group								
Pyrrole								
Furan								

What is claimed is:

1. A pharmaceutical co-crystal composition, comprising: modafinil and a co-crystal former, wherein the co-crystal former is a solid at room temperature, and wherein the modafinil and the co-crystal former are hydrogen bonded to each other.

2. The pharmaceutical co-crystal composition according to claim 1, wherein:

(a) the co-crystal former is selected from a co-crystal former of Table I or Table II;

(b) the co-crystal former has at least one functional group selected from the group consisting of ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(c) the solubility of the co-crystal is increased as compared to the modafinil;

(d) the dose response of the co-crystal is increased as compared to the modafinil;

(e) the dissolution of the co-crystal is increased as compared to the modafinil;

(f) the bioavailability of the co-crystal is increased as compared to the modafinil; or

(g) the stability of the co-crystal is increased as compared to the modafinil.

3. A pharmaceutical co-crystal composition, comprising: modafinil, a co-crystal former, and a third molecule; wherein the co-crystal former is a solid at room temperature, and wherein the modafinil and the third molecule are bonded to each other,

and further wherein the co-crystal former and the third molecule are hydrogen bonded to each other.

4. The pharmaceutical co-crystal composition according to claim 3, wherein:

(a) the co-crystal former is selected from a co-crystal former of Table I or Table II;

(b) the co-crystal former has at least one functional group selected from the group consisting of ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine; or

(c) the solubility of the co-crystal is increased as compared to the modafinil;

(d) the dose response of the co-crystal is increased as compared to the modafinil;

(e) the dissolution of the co-crystal is increased as compared to the modafinil;

(f) the bioavailability of the co-crystal is increased as compared to the modafinil; or

(g) the stability of the co-crystal is increased as compared to the modafinil.

5. A pharmaceutical co-crystal composition, comprising: modafinil and a second API, wherein the second API is either a liquid or a solid at room temperature, and wherein the modafinil and the second API are hydrogen bonded to a molecule.

6. The pharmaceutical co-crystal composition according to claim 5, wherein:

(a) the modafinil is hydrogen bonded to the second API;

(b) the second API is a liquid at room temperature;

(c) the second API is a solid at room temperature;

(d) the second API has at least one functional group selected from the group consisting of ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(e) the solubility of the co-crystal is increased as compared to the modafinil;

(f) the dose response of the co-crystal is increased as compared to the modafinil;

(g) the dissolution of the co-crystal is increased as compared to the modafinil;

(h) the bioavailability of the co-crystal is increased as compared to the modafinil; or

(i) the stability of the co-crystal is increased as compared to the modafinil.

7. The pharmaceutical co-crystal composition according to claim 1, further comprising a pharmaceutically acceptable diluent, excipient, or carrier.

8. A co-crystal comprising modafinil and a co-crystal former selected from the group consisting of: malonic acid, benzamide, mandelic acid, glycolic acid, fumaric acid, and maleic acid.

9. A co-crystal according to claim 8, wherein:

(a) the co-crystal is characterized by a powder X-ray diffraction pattern comprising peaks expressed in terms of 2 theta angles, wherein:

(i) said form is a modafinil:malonic acid co-crystal and said X-ray diffraction pattern comprises peaks at 5.00, 9.17, and 22.77 degrees;

(ii) said form is a modafinil:malonic acid co-crystal and said X-ray diffraction pattern comprises peaks at 16.81, 19.43, and 28.45 degrees;

(iii) said form is a modafinil:malonic acid co-crystal and said X-ray diffraction pattern comprises peaks at 5.00, 18.26, and 21.94 degrees;

(iv) said form is a modafinil:malonic acid co-crystal and said X-ray diffraction pattern comprises peaks at 21.36, 21.94, and 24.49 degrees;

(v)

(vi) said form is a modafinil:glycolic acid co-crystal and said X-ray diffraction pattern comprises peaks at 9.51, 15.97, and 20.03 degrees;

(vii) said form is a modafinil:glycolic acid co-crystal and said X-ray diffraction pattern comprises peaks at 9.51, 25.03, and 25.71 degrees;

(viii) said form is a modafinil:glycolic acid co-crystal and said X-ray diffraction pattern comprises peaks at 19.01, 21.59, and 23.75 degrees;

(ix) said form is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises peaks at 6.15, 9.61, and 19.97 degrees;

(x) said form is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises peaks at 9.61, 10.23, 19.97, and 21.83 degrees;

(xi) said form is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises peaks at 4.69, 18.01, and 22.45 degrees; or

(xii) said form is a modafinil:maleic acid co-crystal and said X-ray diffraction pattern comprises peaks at 15.65, 16.53, and 17.19 degrees; or

(b) the co-crystal is characterized by an endothermic transition observed using DSC analysis wherein:

(i) said form is a modafinil:malonic acid co-crystal and said endothermic transition is 106.23 +/- 2.0 degrees C; or

(ii) said form is a modafinil:maleic acid co-crystal and said endothermic transition is 167.67 +/- 2.0 degrees C.

10. A process for preparing a pharmaceutical co-crystal composition comprising modafinil and a co-crystal former, comprising:

(a) providing modafinil and a co-crystal former, wherein the co-crystal former is a solid at room temperature;

(b) grinding, heating, co-subliming, co-melting, or contacting in solution the modafinil with the co-crystal former under crystallization conditions, so as to form a solid phase, wherein the modafinil and co-crystal former are hydrogen bonded to each other;

(c) isolating co-crystals formed thereby; and

(d) incorporating the co-crystals into a pharmaceutical composition.

11. The process of claim 10, wherein:

(a) the co-crystal former is selected from a co-crystal former of Table I or Table II; or

(b) the co-crystal former has at least one functional group selected from the group consisting of ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine.

12. A process for preparing a pharmaceutical co-crystal composition comprising modafinil, a co-crystal former, and a third molecule, comprising:

(a) providing modafinil and a co-crystal former, wherein the co-crystal former is a solid at room temperature;

(b) grinding, heating, co-subliming, co-melting, or contacting in solution the modafinil with the co-crystal former under crystallization conditions, so as to form a solid phase, wherein the modafinil and the third molecule are bonded to each other, and further wherein the co-crystal former and the third molecule are hydrogen bonded to each other;

(c) isolating co-crystals formed thereby; and

(d) incorporating the co-crystals into a pharmaceutical composition.

13. The process of claim 12, wherein:

(a) the co-crystal former is selected from a co-crystal former of Table I or Table II; or

(b) the co-crystal former has at least one functional group selected from the group consisting of ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine.

14. A process for preparing a pharmaceutical co-crystal composition comprising modafinil and a second API, comprising:

(a) providing modafinil and a second API, wherein the second API is either a liquid or a solid at room temperature;

(b) grinding, heating, co-subliming, co-melting, or contacting in solution the modafinil and the second API under crystallization conditions, so as to form

a solid phase, wherein the modafinil and the second API are hydrogen bonded to a molecule;

(c) isolating co-crystals formed thereby; and

(d) incorporating the co-crystals into a pharmaceutical composition.

15. The process of claim 14, wherein:

(a) modafinil is hydrogen bonded to the second API;

(b) the second API is a liquid at room temperature;

(c) the second API is a solid at room temperature; or

(d) the second API has at least one functional group selected from the group consisting of ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile, diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine.

16. The process of claim 10, further comprising: incorporating a pharmaceutically acceptable diluent, excipient, or carrier.

17. A process of preparing a co-crystal comprising modafinil and a co-crystal former, comprising:

(a) providing modafinil and a co-crystal former;

(b) grinding, heating, co-subliming, co-melting, or contacting in solution the modafinil with the co-crystal former under crystallization conditions, so as to form a solid phase; and

(c) isolating co-crystals formed thereby;

wherein the co-crystal former is selected from the group consisting of malonic acid, benzamide, mandelic acid, glycolic acid, fumaric acid, and maleic acid.

18. A process for modulating the solubility of modafinil for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the modafinil with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the modafinil and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has a modulated solubility as compared to the modafinil; and

(c) incorporating the co-crystal having modulated solubility into a pharmaceutical composition.

19. The process of claim 18, wherein the solubility of the co-crystal is increased as compared to the modafinil.

20. A process for modulating the dose response of modafinil for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the modafinil with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the modafinil and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has a modulated dose response as compared to the modafinil; and

(c) incorporating the co-crystal having modulated dose response into a pharmaceutical composition.

21. The process of claim 20, wherein the dose response of the co-crystal is increased as compared to the modafinil.

22. A process for modulating the dissolution of modafinil for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the modafinil with a co-crystal forming compound under

crystallization conditions, so as to form a co-crystal of the modafinil and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has a modulated dissolution as compared to the modafinil; and

(c) incorporating the co-crystal having modulated dissolution into a pharmaceutical composition.

23. The process of claim 22, wherein the dissolution of the co-crystal is increased as compared to the modafinil.

24. A process for modulating the bioavailability of modafinil for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the modafinil with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the modafinil and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has a modulated bioavailability as compared to the modafinil; and

(c) incorporating the co-crystal having modulated bioavailability into a pharmaceutical composition.

25. The process of claim 24, wherein the bioavailability of the co-crystal is increased as compared to the modafinil.

26. A process for increasing the stability of modafinil for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution the modafinil with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the modafinil and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has increased stability as compared to the modafinil; and

(c) incorporating the co-crystal having increased stability into a pharmaceutical composition.

27. A process for modulating the morphology of modafinil for use in a pharmaceutical composition, which process comprises:

(a) grinding, heating, co-subliming, co-melting, or contacting in solution modafinil with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the modafinil and the co-crystal forming compound;

(b) isolating the co-crystal, wherein the co-crystal has a different morphology as compared to the modafinil; and

(c) incorporating the co-crystal having modulated morphology into a pharmaceutical composition.

28. An acetic acid solvate of modafinil.

29. A pharmaceutical composition comprising an acetic acid solvate of modafinil.

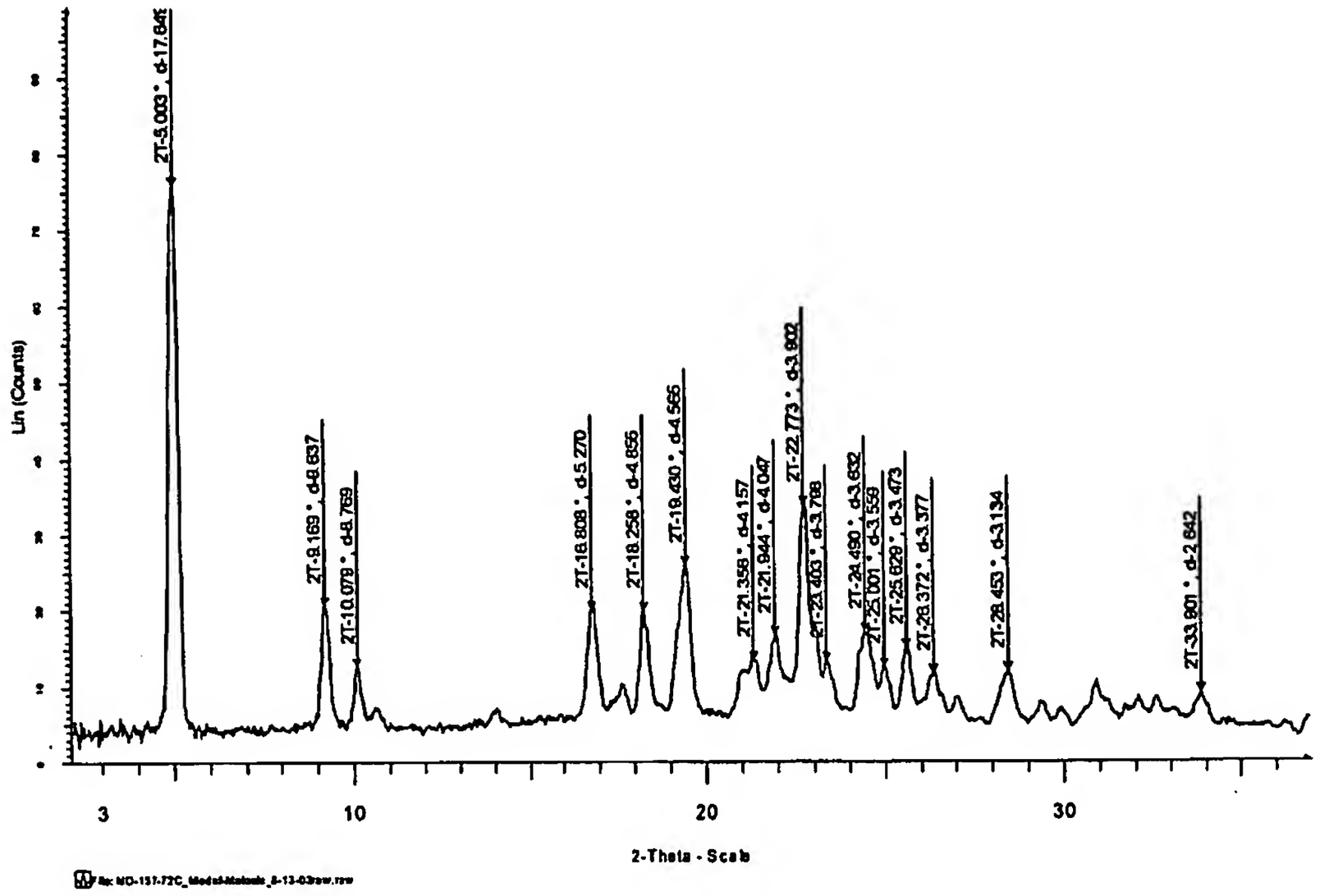
30. The pharmaceutical composition according to claim 29, further comprising a pharmaceutically acceptable diluent, excipient, or carrier.

31. A method for treating a subject suffering from excessive daytime sleepiness associated with narcolepsy, which comprises administering to a subject a therapeutically effective amount of a co-crystal comprising modafinil.

32. The method according to claim 30, wherein the subject is a human subject.

Abstract

Co-crystals, solvates, and polymorphs of modafinil are formed and many important physical properties are altered. The solubility, dissolution, bioavailability, dose response, and stability of modafinil can be modulated to improve efficacy in pharmaceutical compositions.



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33.901

Figure 1

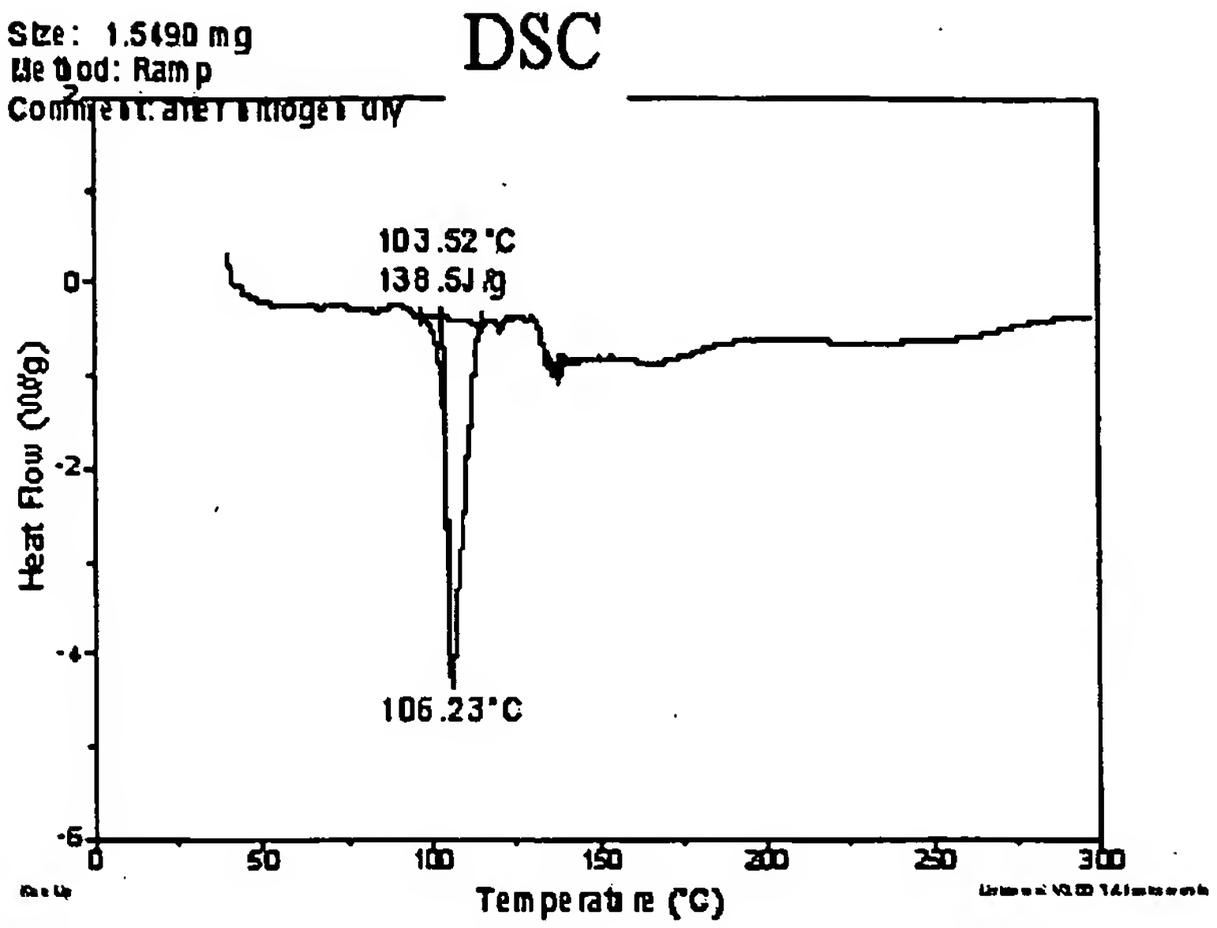

Figure 2

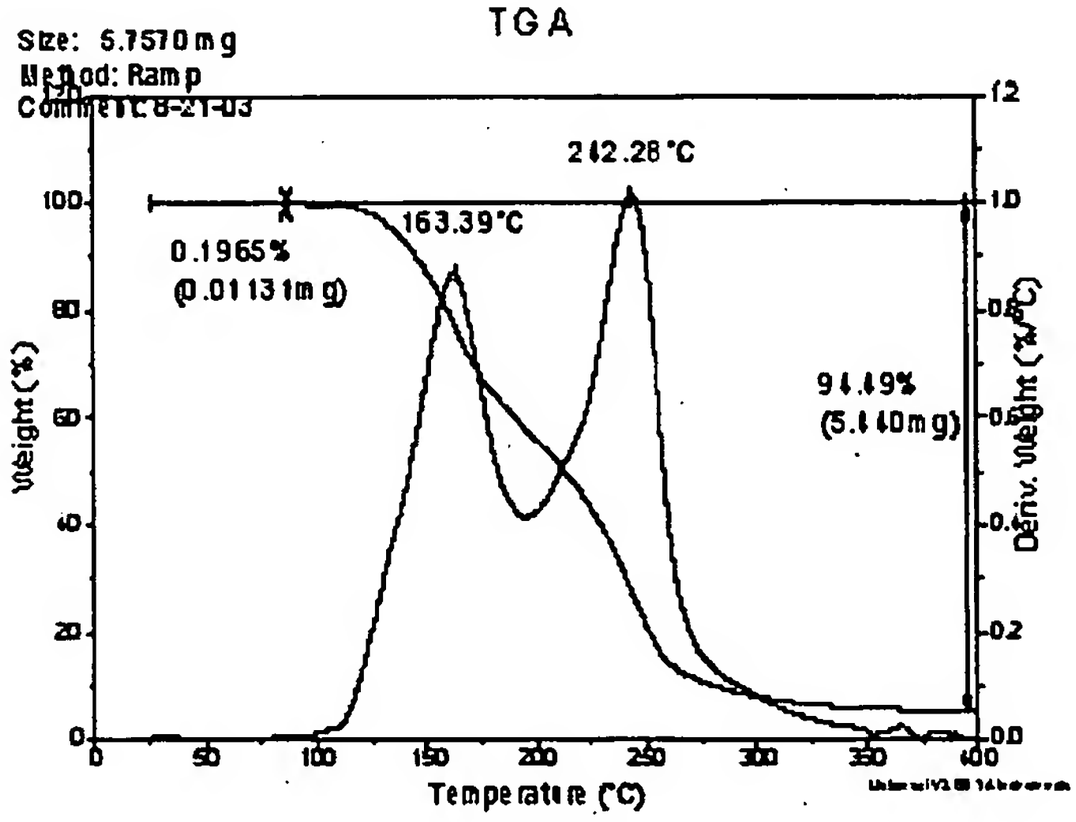

Figure 3

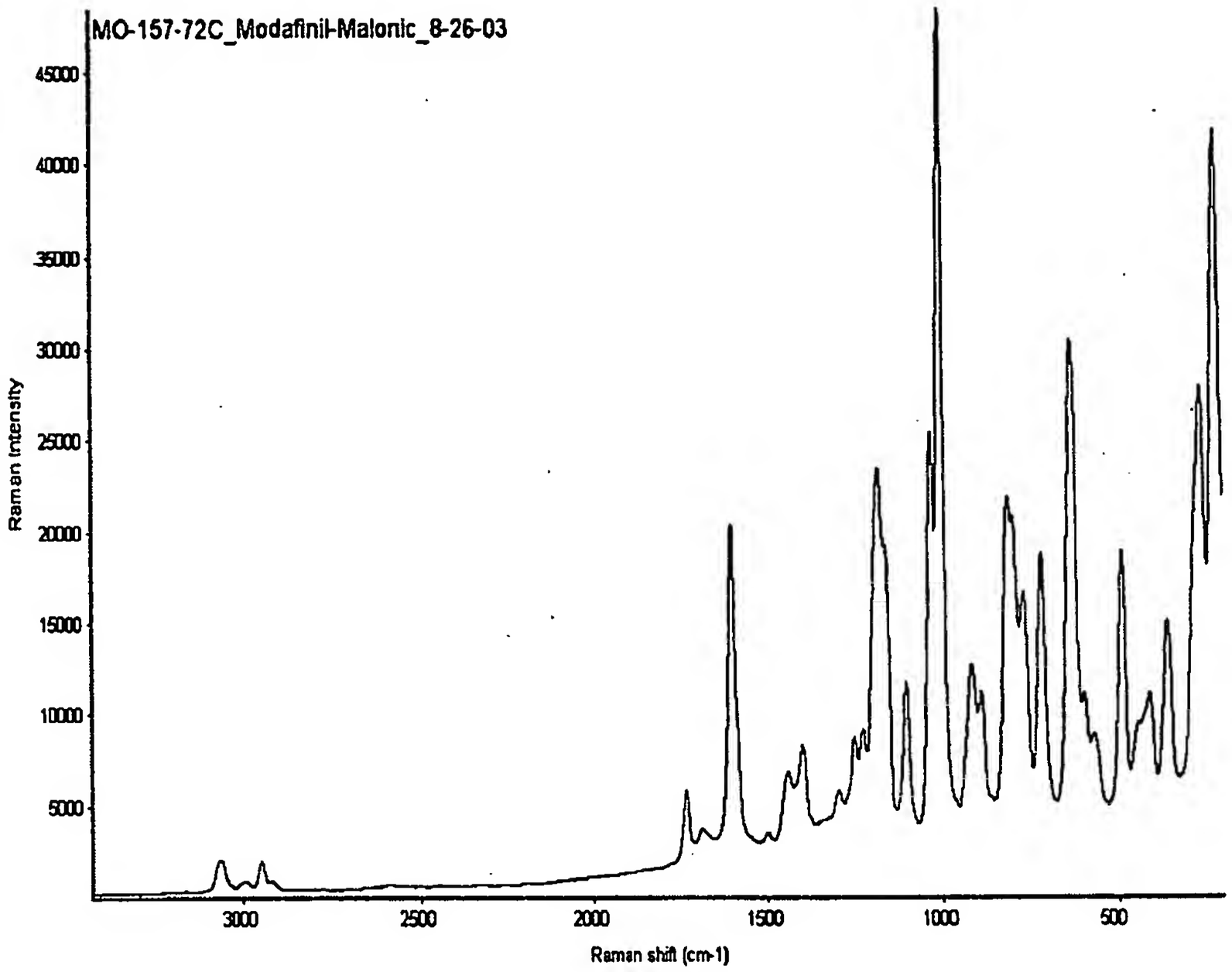

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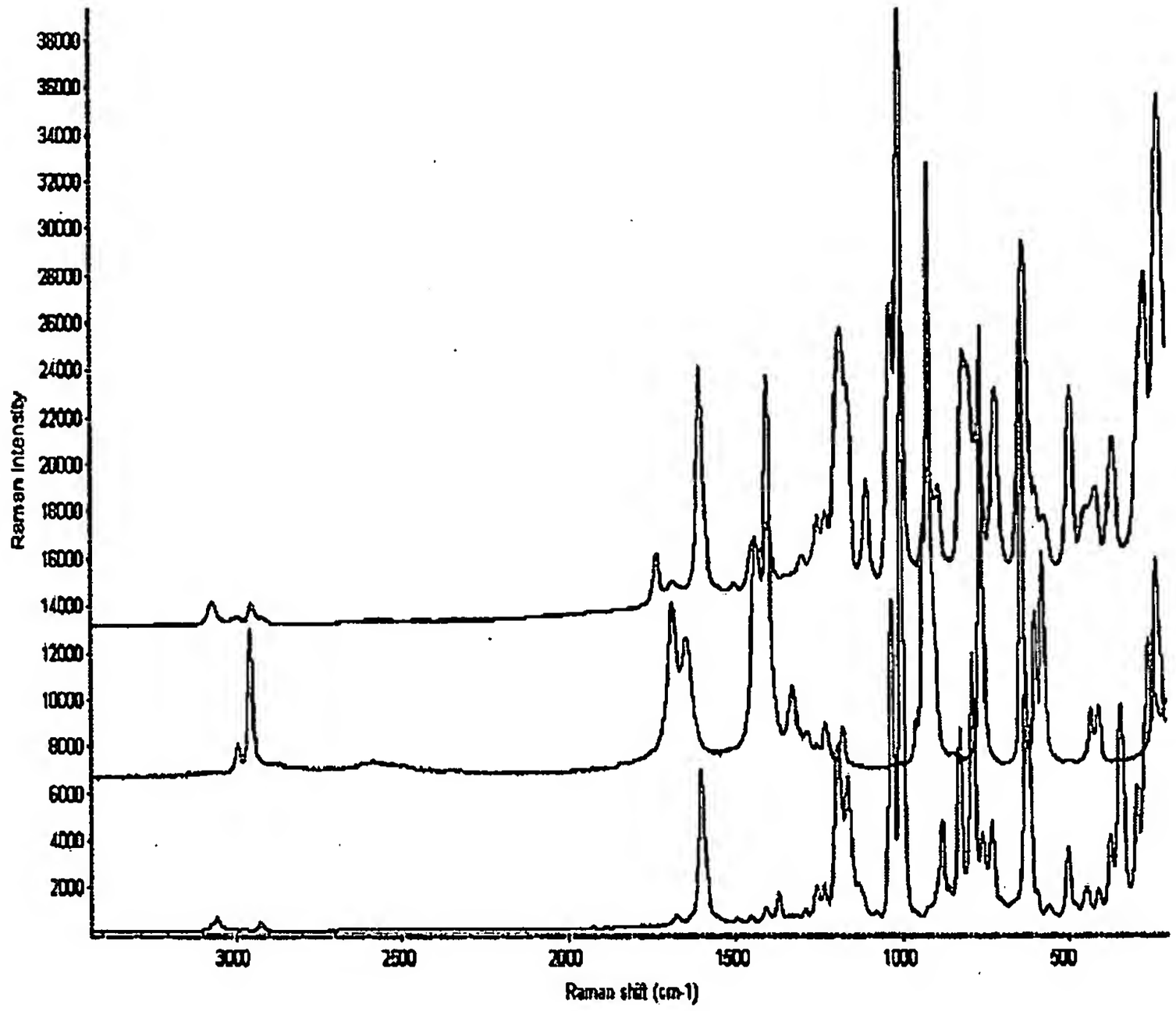
Figure 4A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2000
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Raman shift (cm-1)

Figure 4B

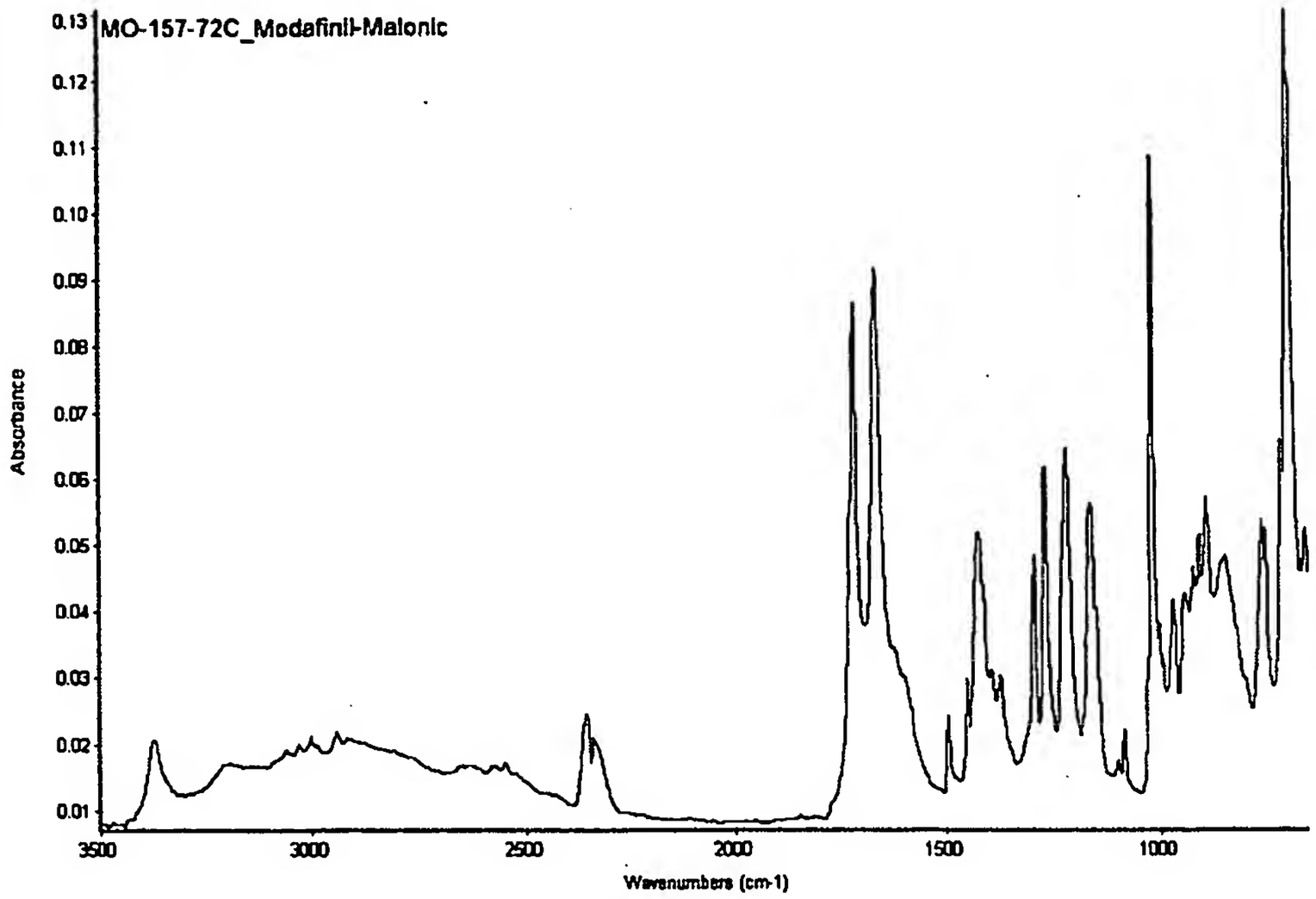

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Figure 5A

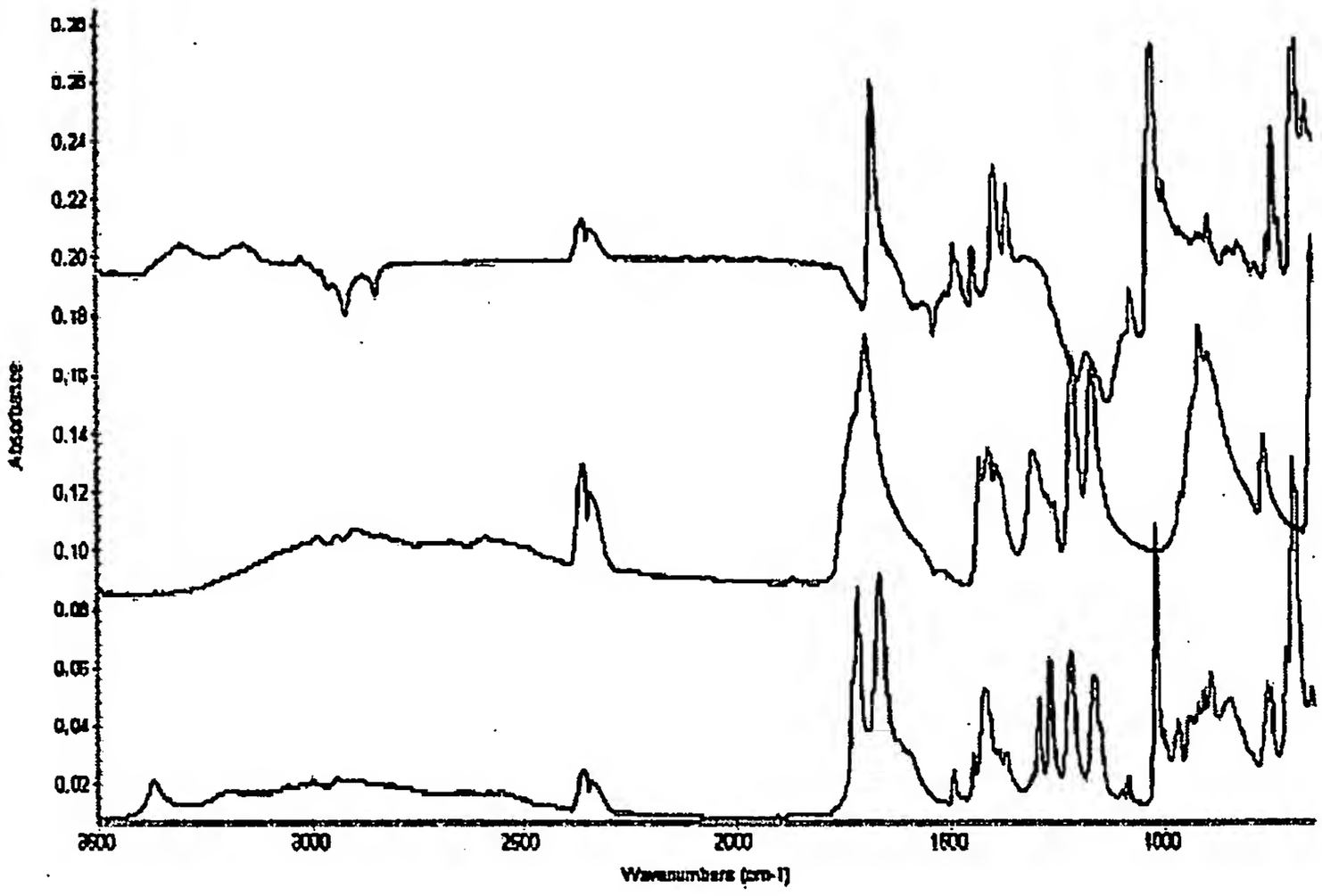


Figure 5B

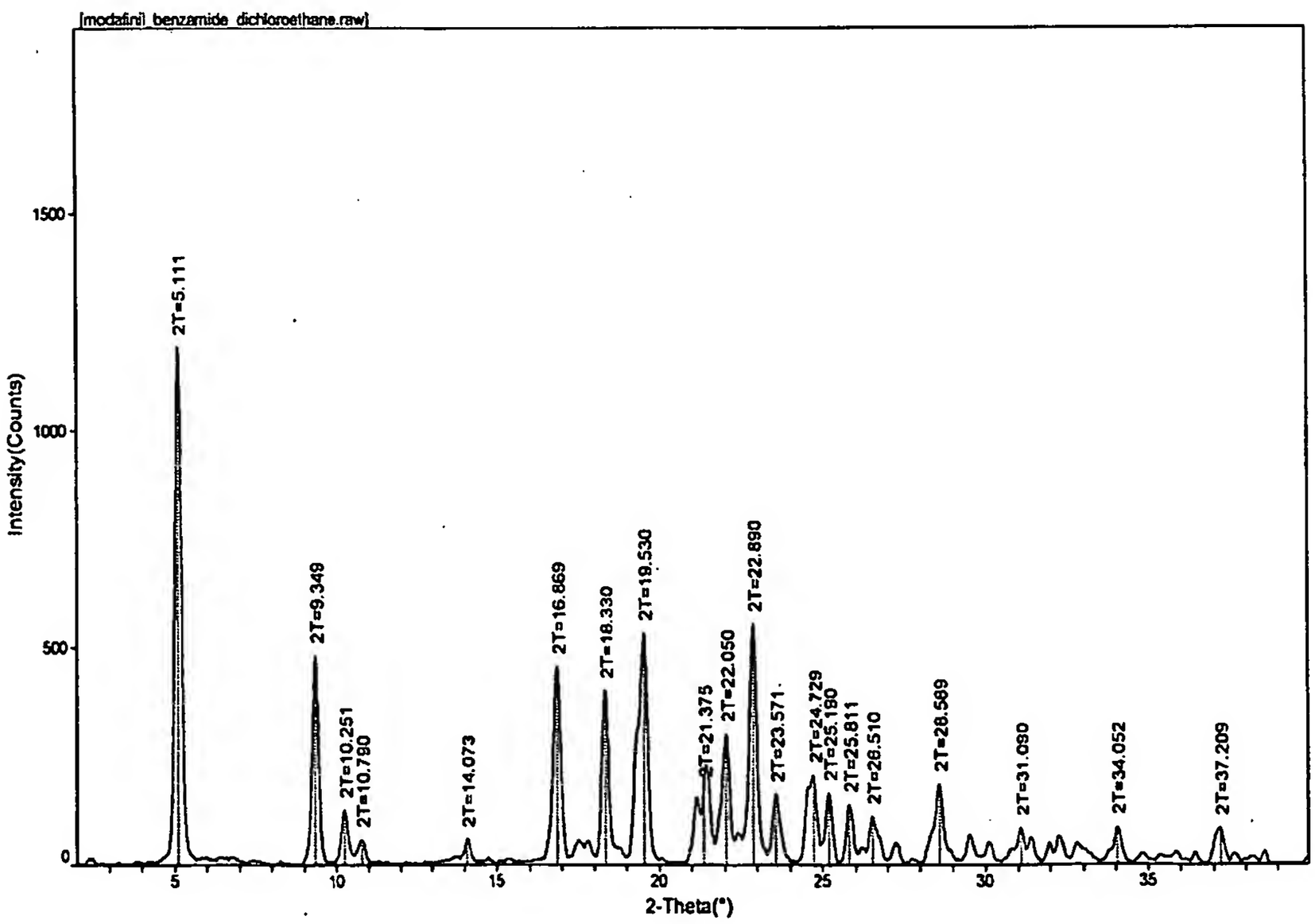


Figure 6

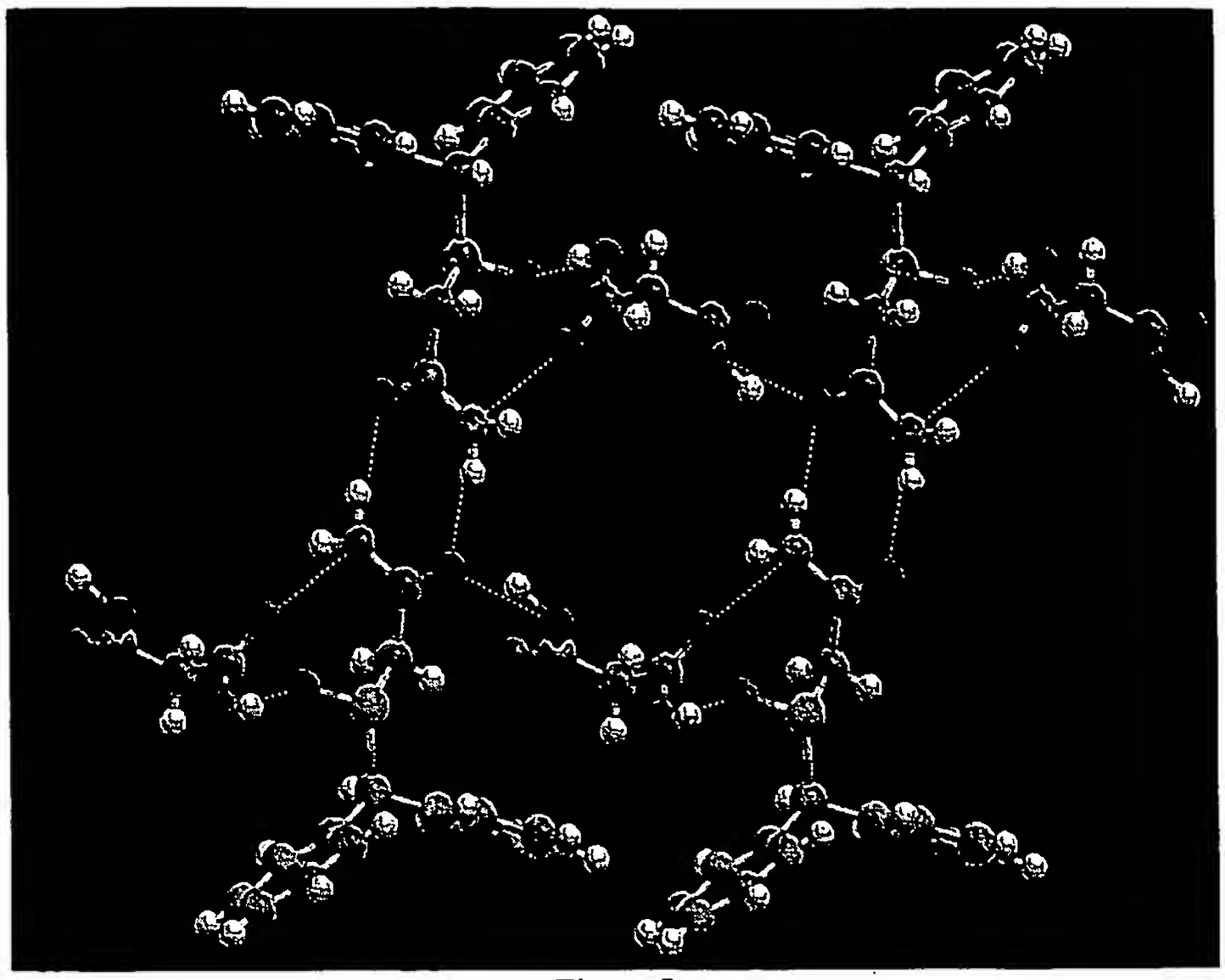


Figure 7

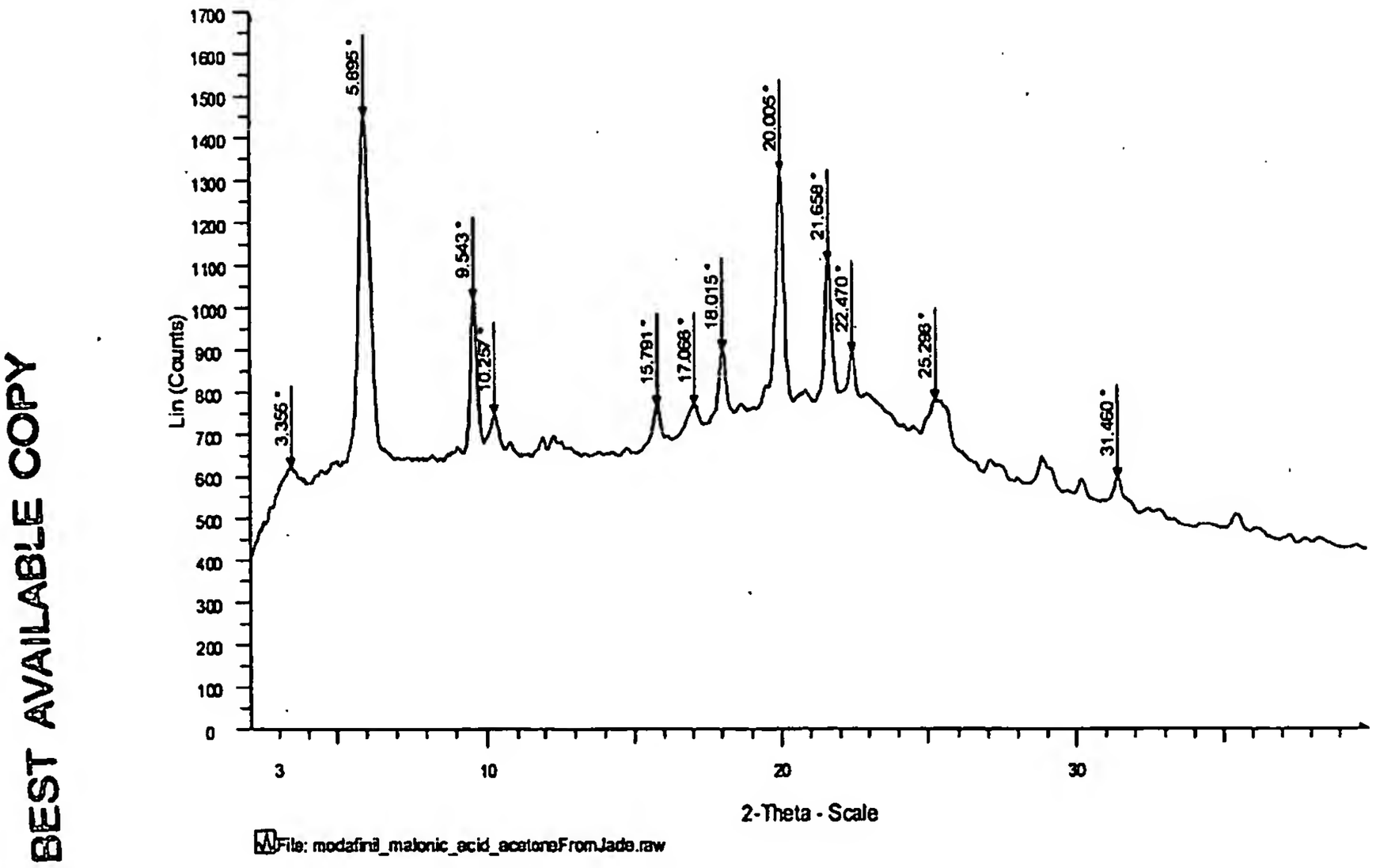


Figure 8

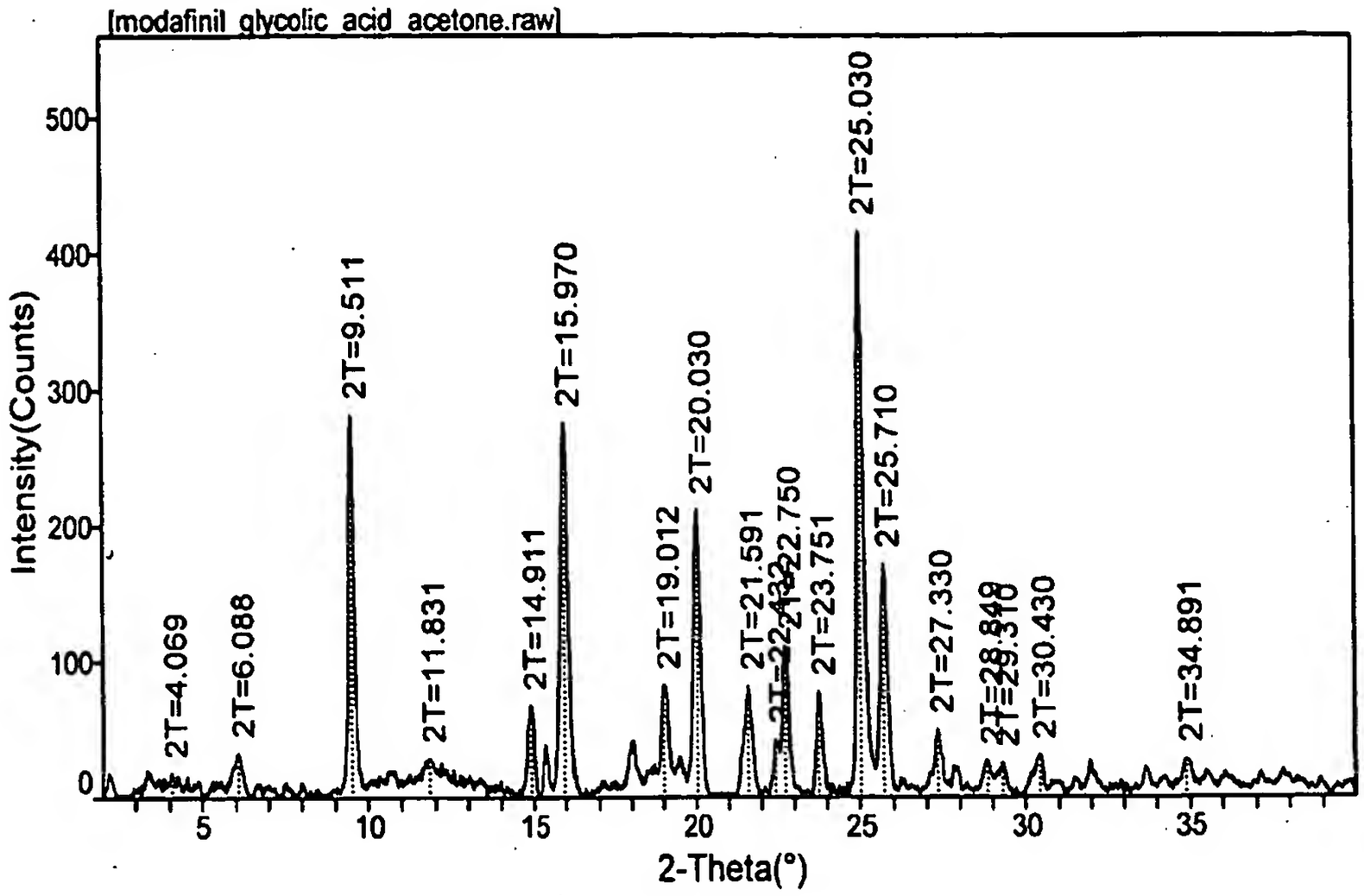


Figure 9A

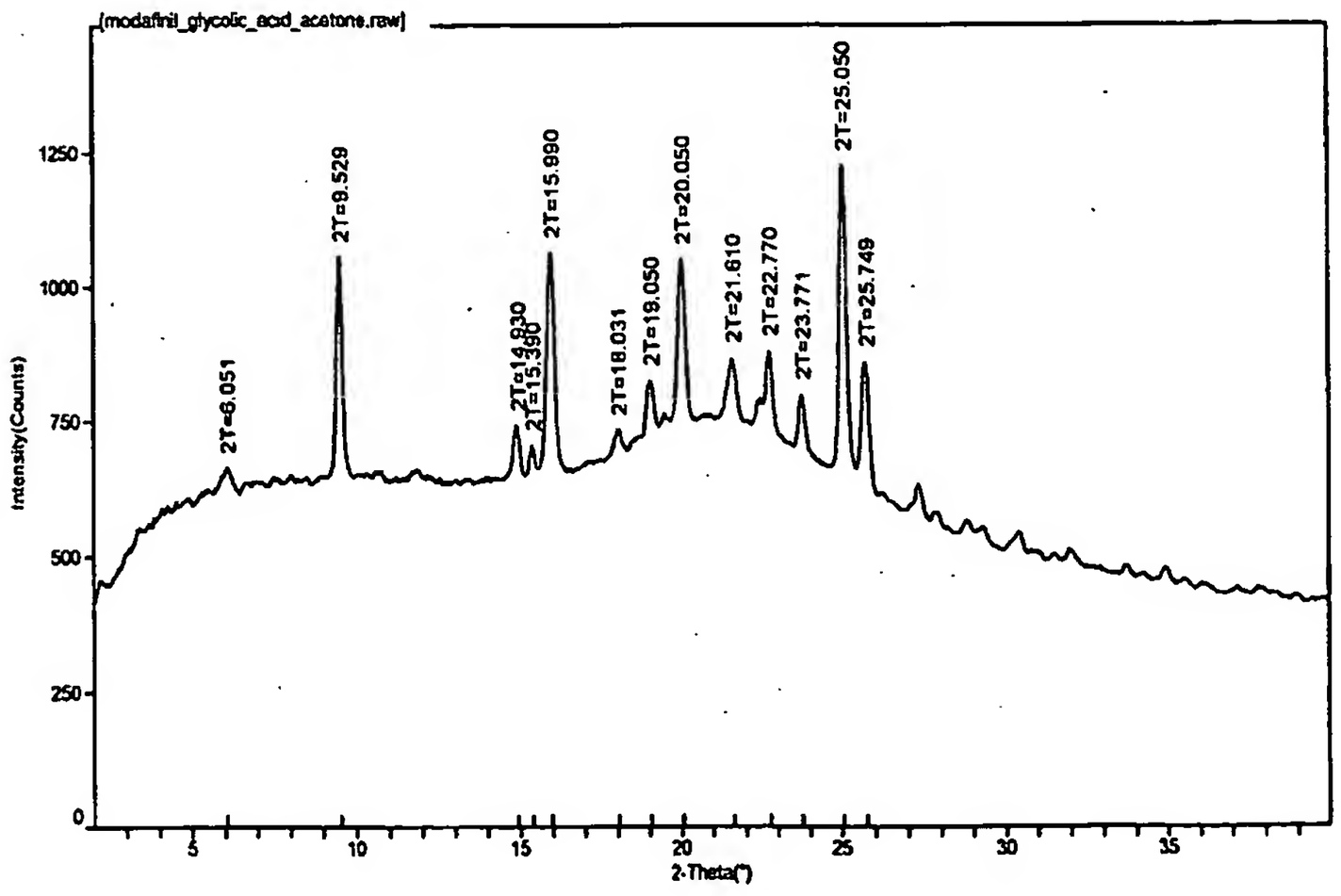
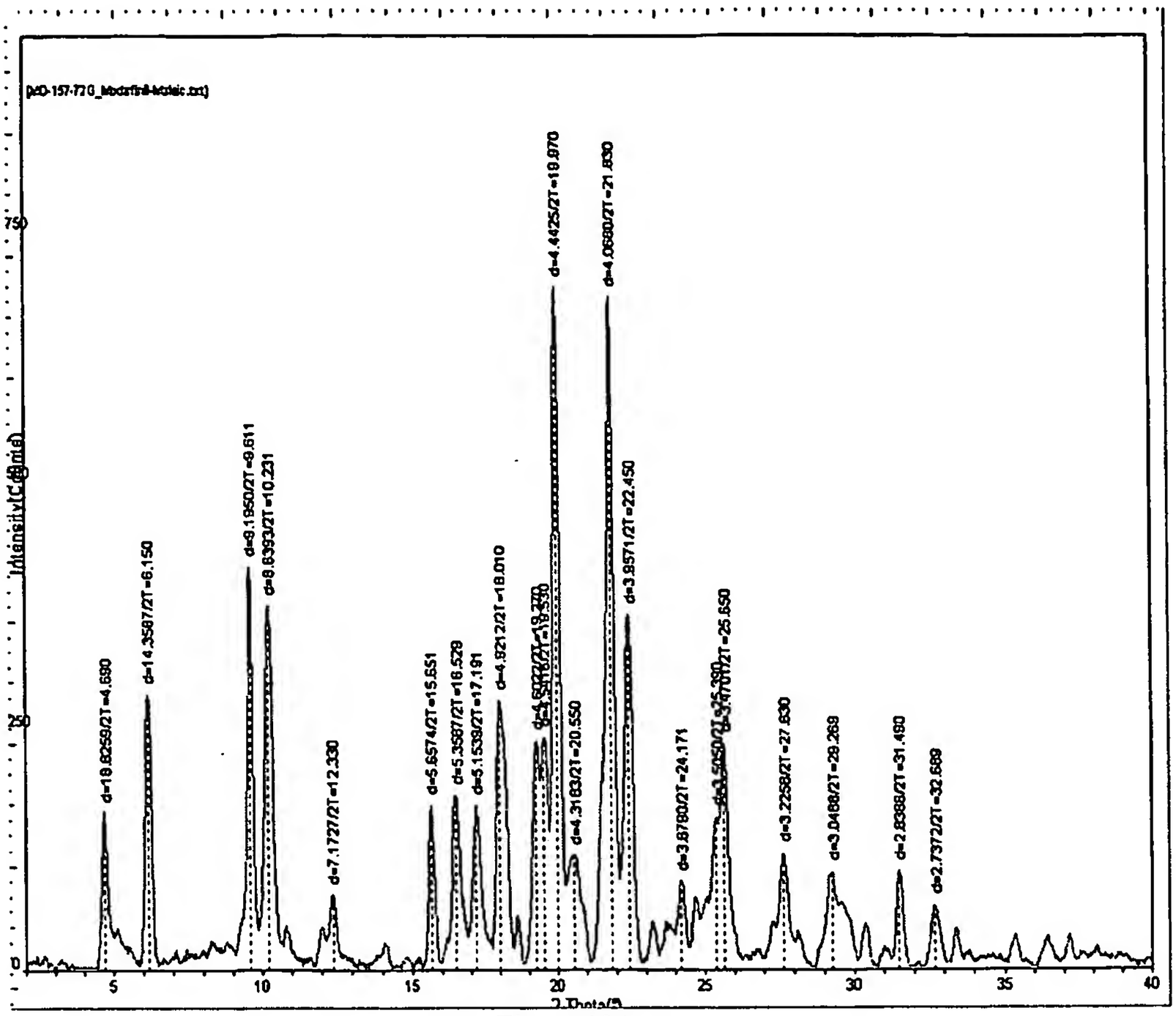


Figure 9B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d=8.839/2T=10.231
d=7.172/2T=12.330
d=5.657/2T=15.651
d=5.358/2T=16.529
d=5.153/2T=17.191
d=4.921/2T=18.010
d=4.316/2T=20.550
d=3.957/2T=22.450
d=3.878/2T=24.171
d=3.225/2T=27.630
d=3.046/2T=29.269
d=2.839/2T=31.490
d=2.737/2T=32.689
0
5
10
15
20
25
30
35
40

Figure 10A

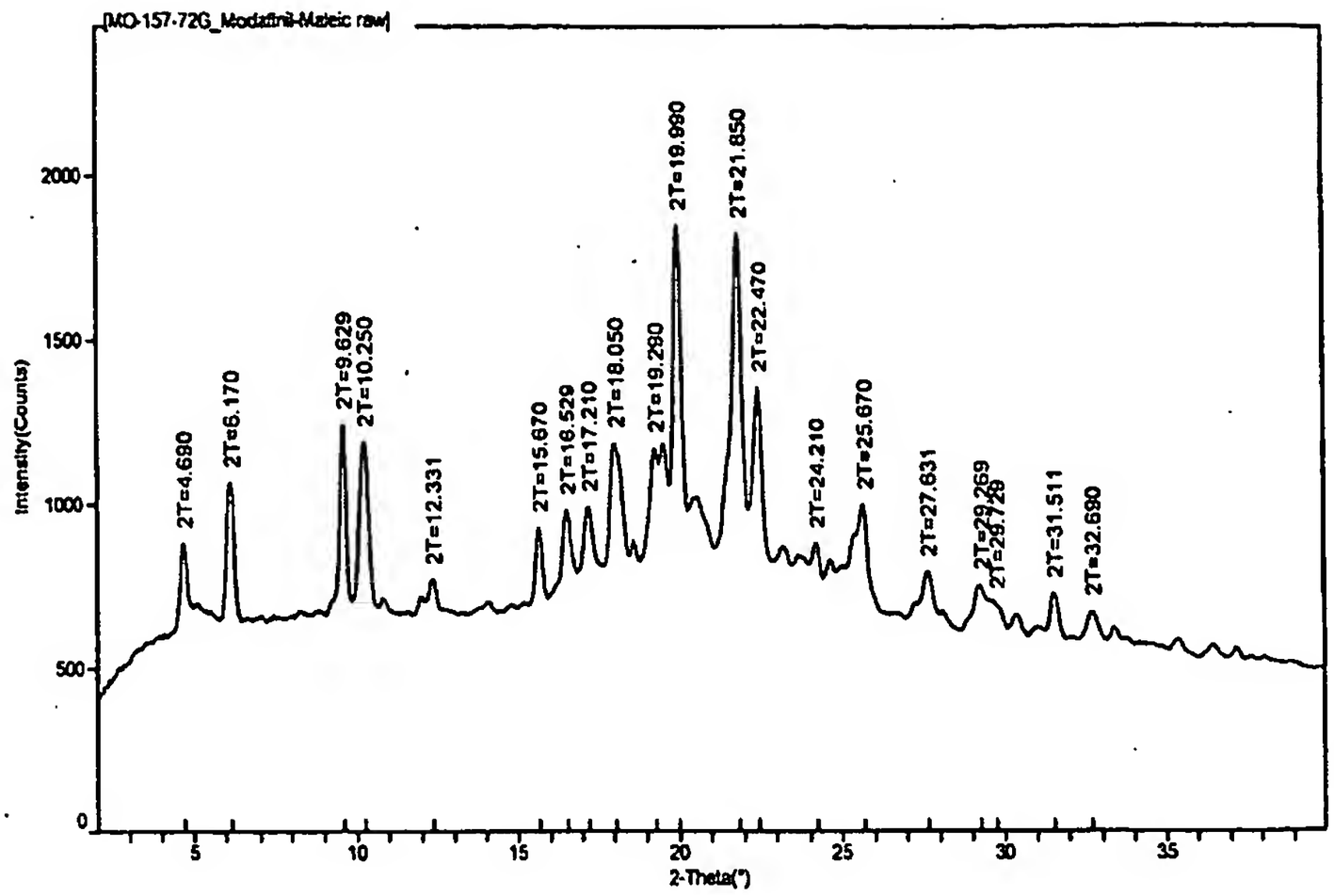


Figure 10B

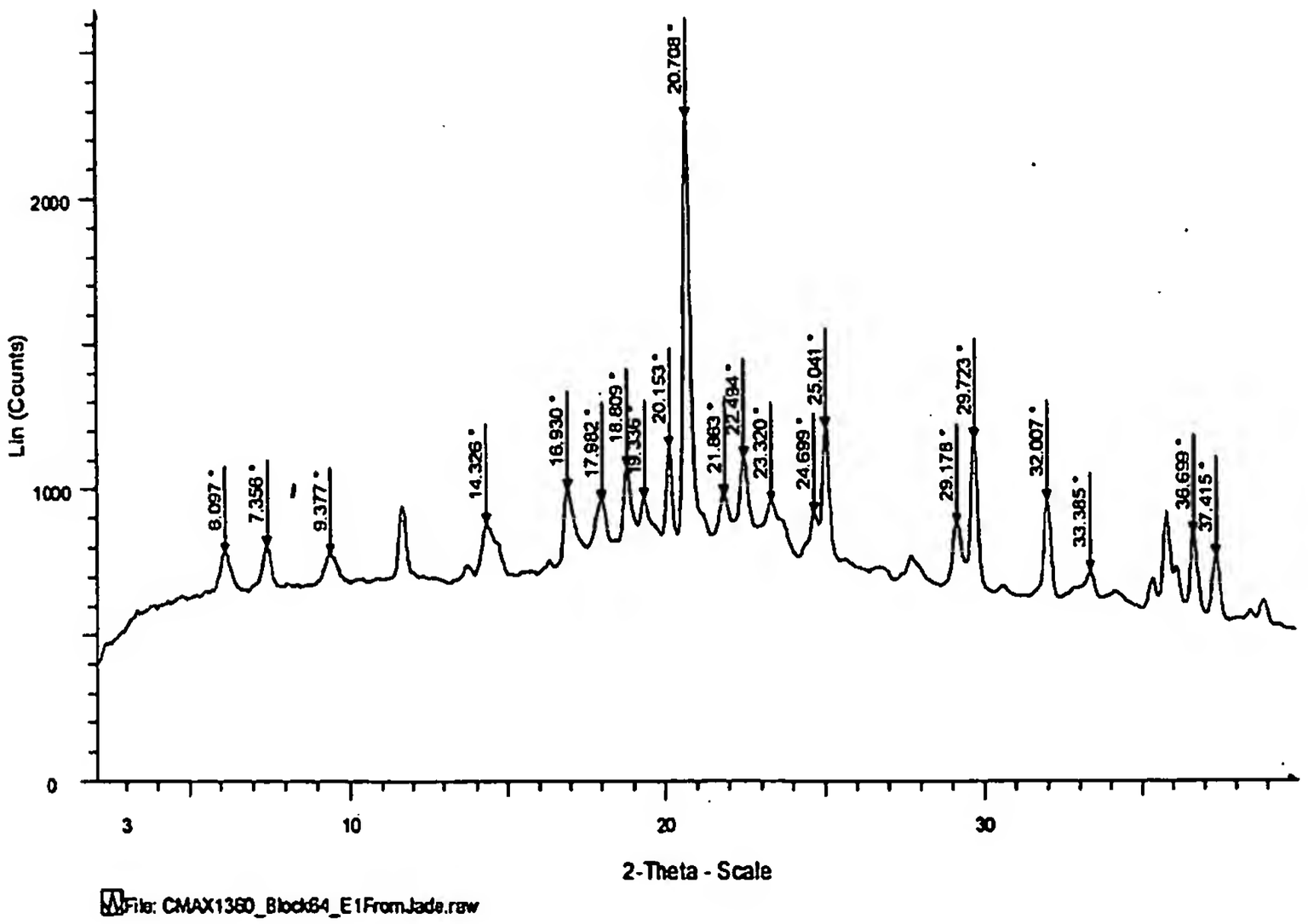


Figure 11

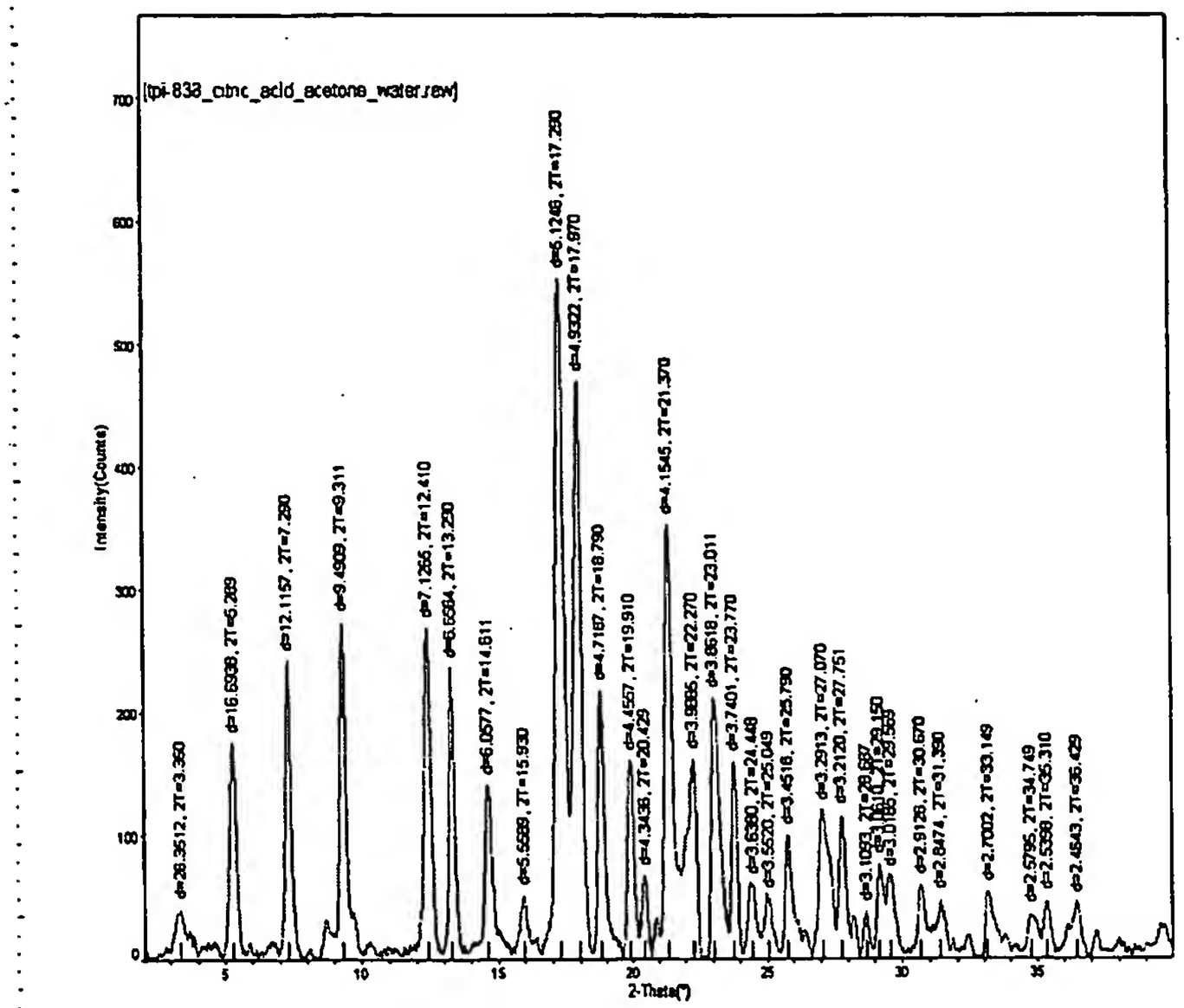

Intensity(Counts)
2-Theta(°)
d=28.3512, 2T=3.350
d=16.6308, 2T=5.289
d=12.1157, 2T=7.290
d=9.4909, 2T=9.311
d=7.1266, 2T=12.410
d=6.6384, 2T=13.290
d=6.0577, 2T=14.611
d=5.5889, 2T=15.930
d=4.9322, 2T=17.970
d=4.7187, 2T=18.790
d=4.4557, 2T=19.910
d=4.3438, 2T=20.429
d=4.1545, 2T=21.370
d=3.9886, 2T=22.270
d=3.8618, 2T=23.011
d=3.7401, 2T=23.770
d=3.6380, 2T=24.448
d=3.5520, 2T=25.049
d=3.4516, 2T=25.790
d=3.2913, 2T=27.070
d=3.2120, 2T=27.751
d=2.9126, 2T=30.670
d=2.8474, 2T=31.390
d=2.7002, 2T=33.149
d=2.5795, 2T=34.749
d=2.5398, 2T=35.310
d=2.4643, 2T=36.429

Figure 12

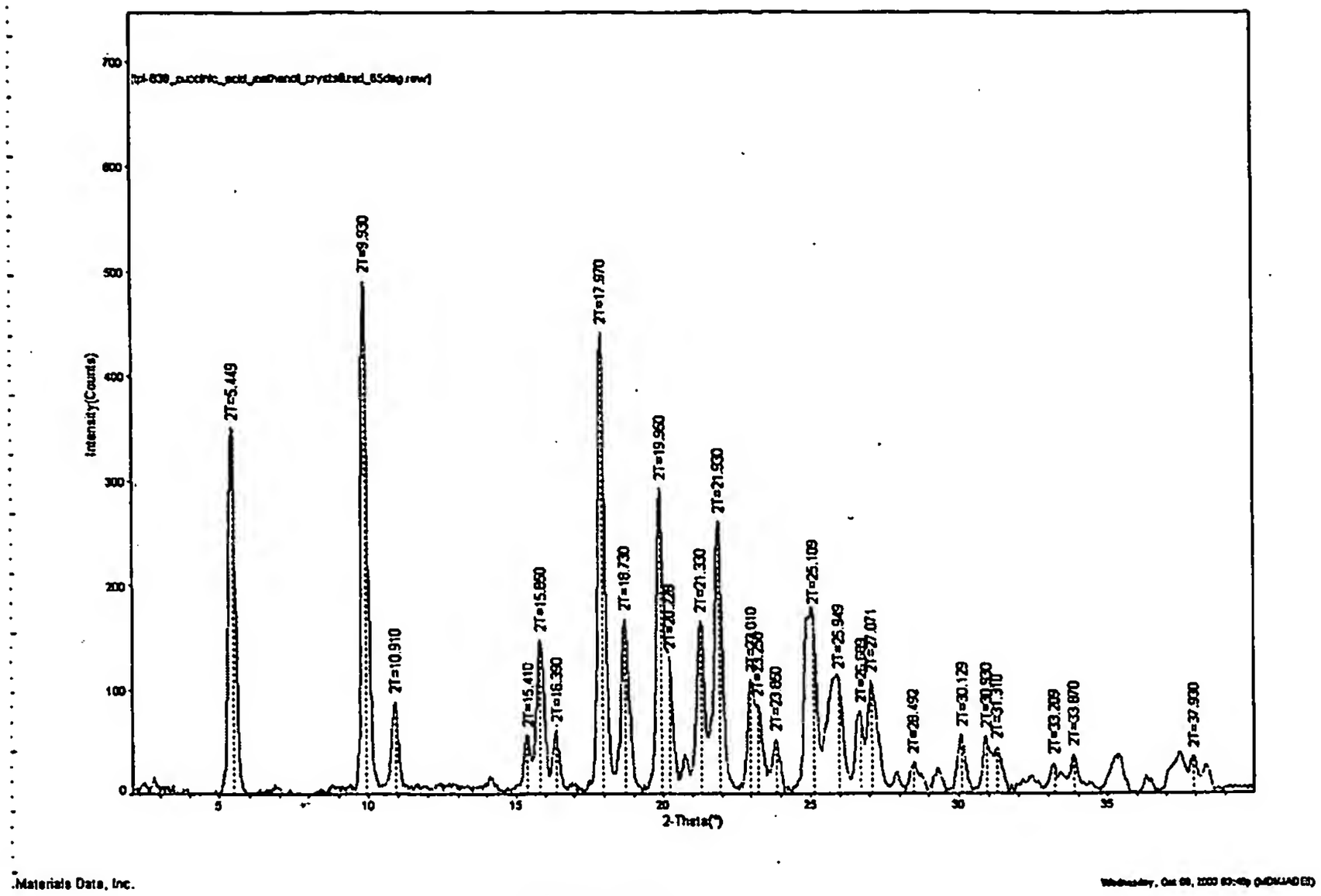


Figure 13A

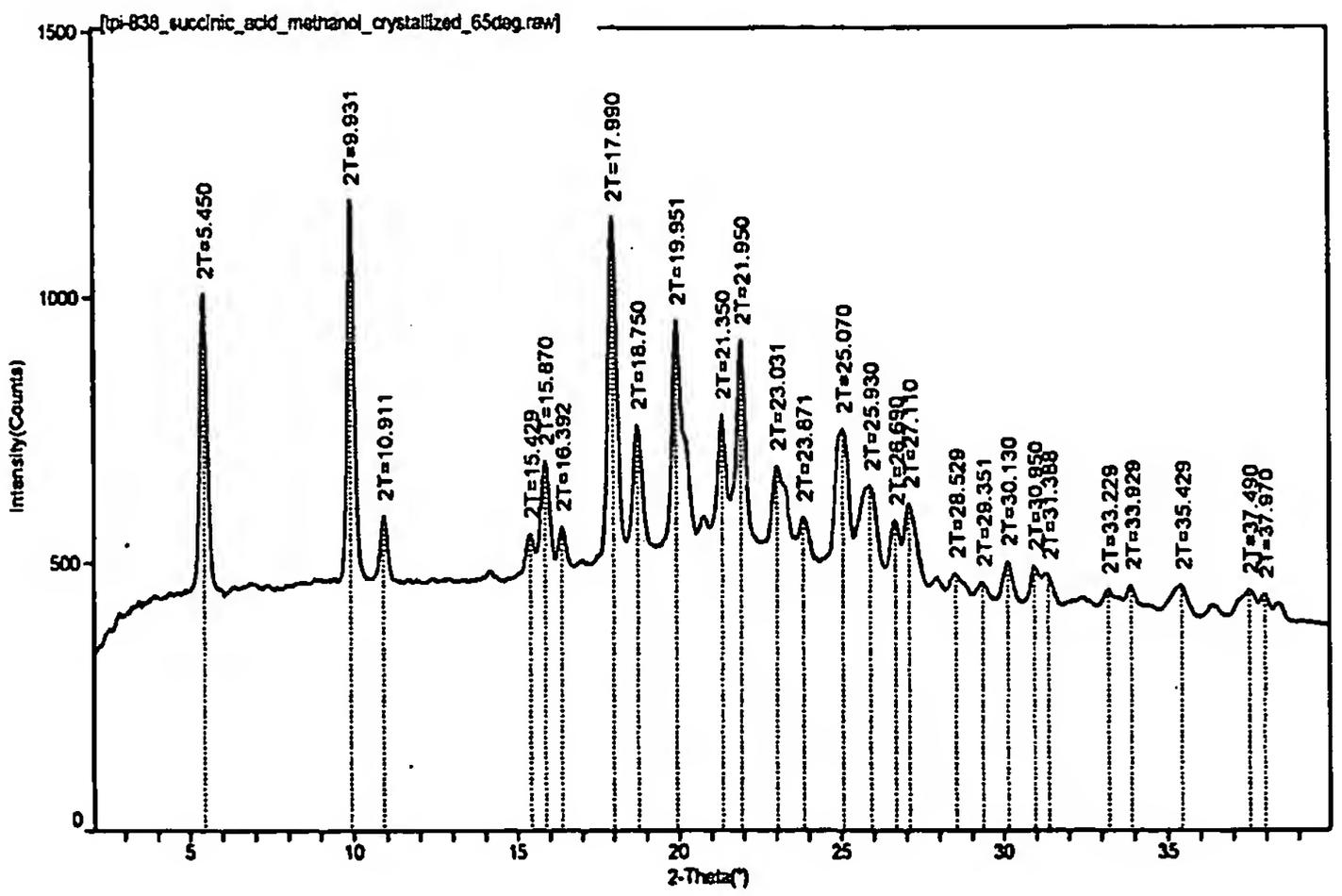


Figure 13B

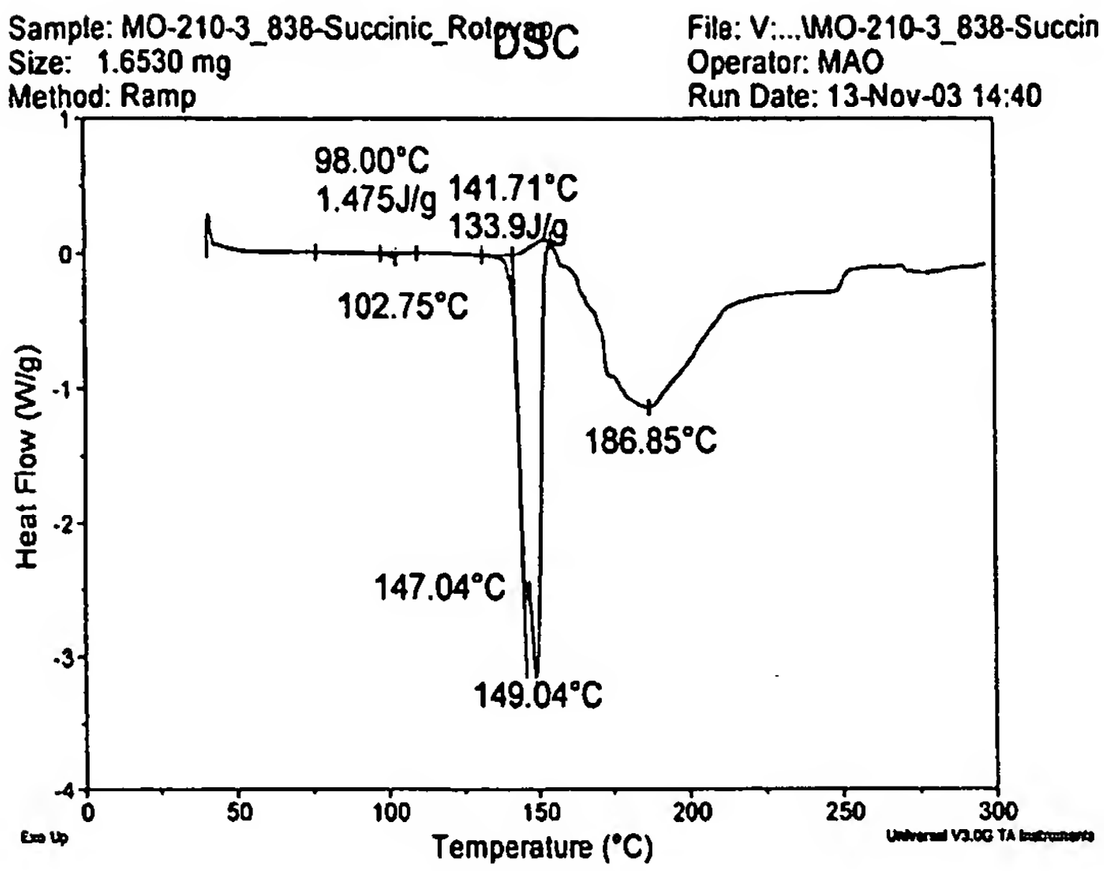


Figure 14

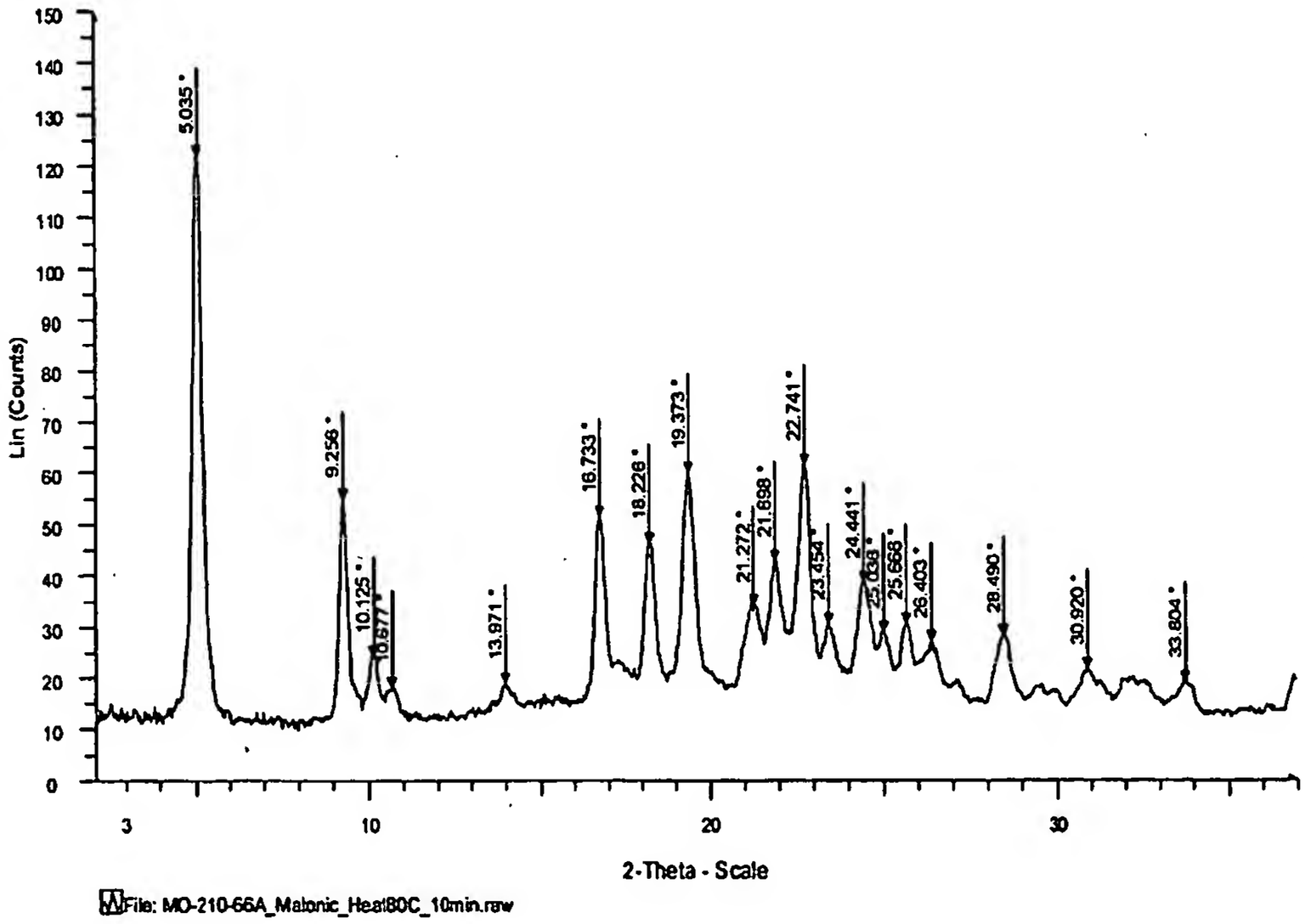


Figure 15

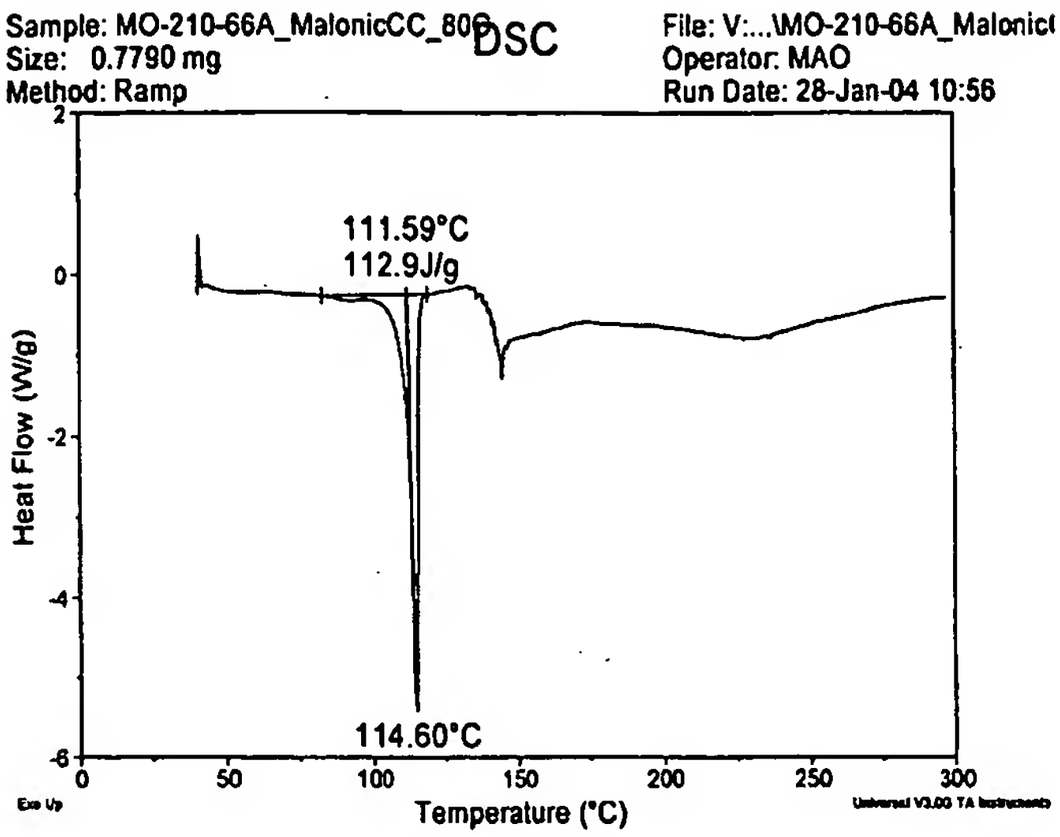


Figure 16

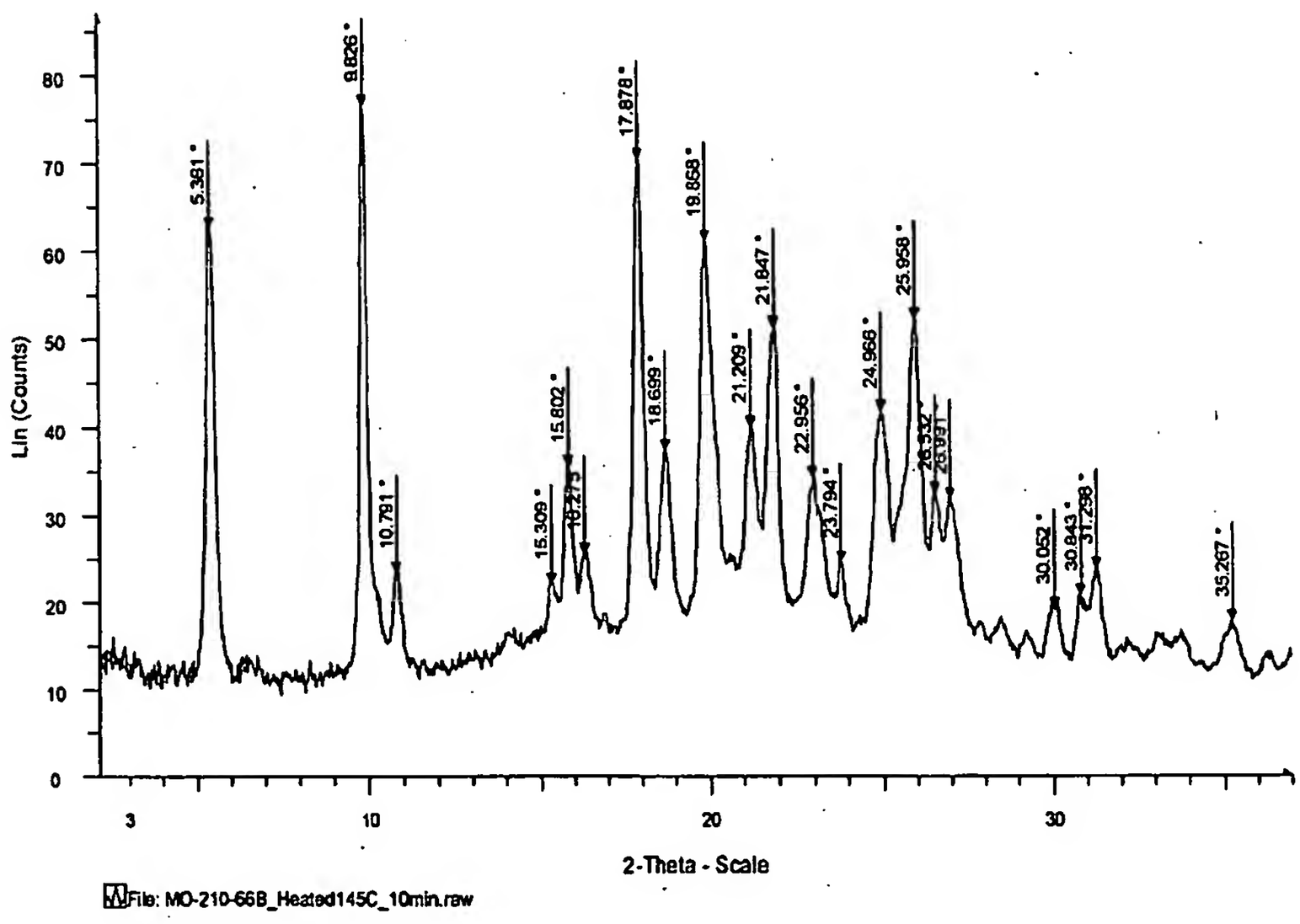


Figure 17

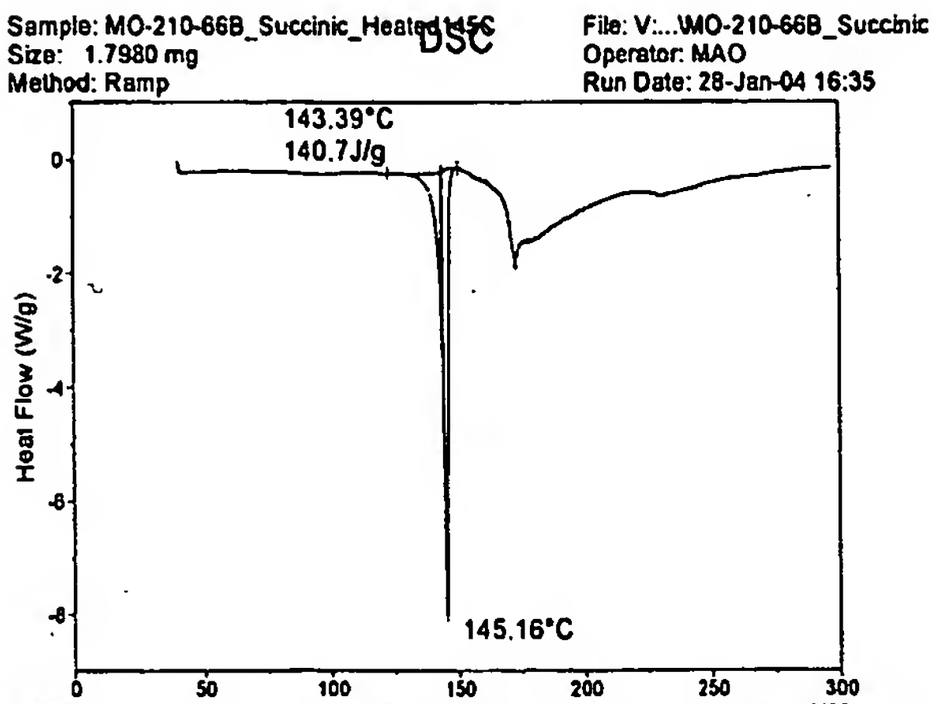


Figure 18

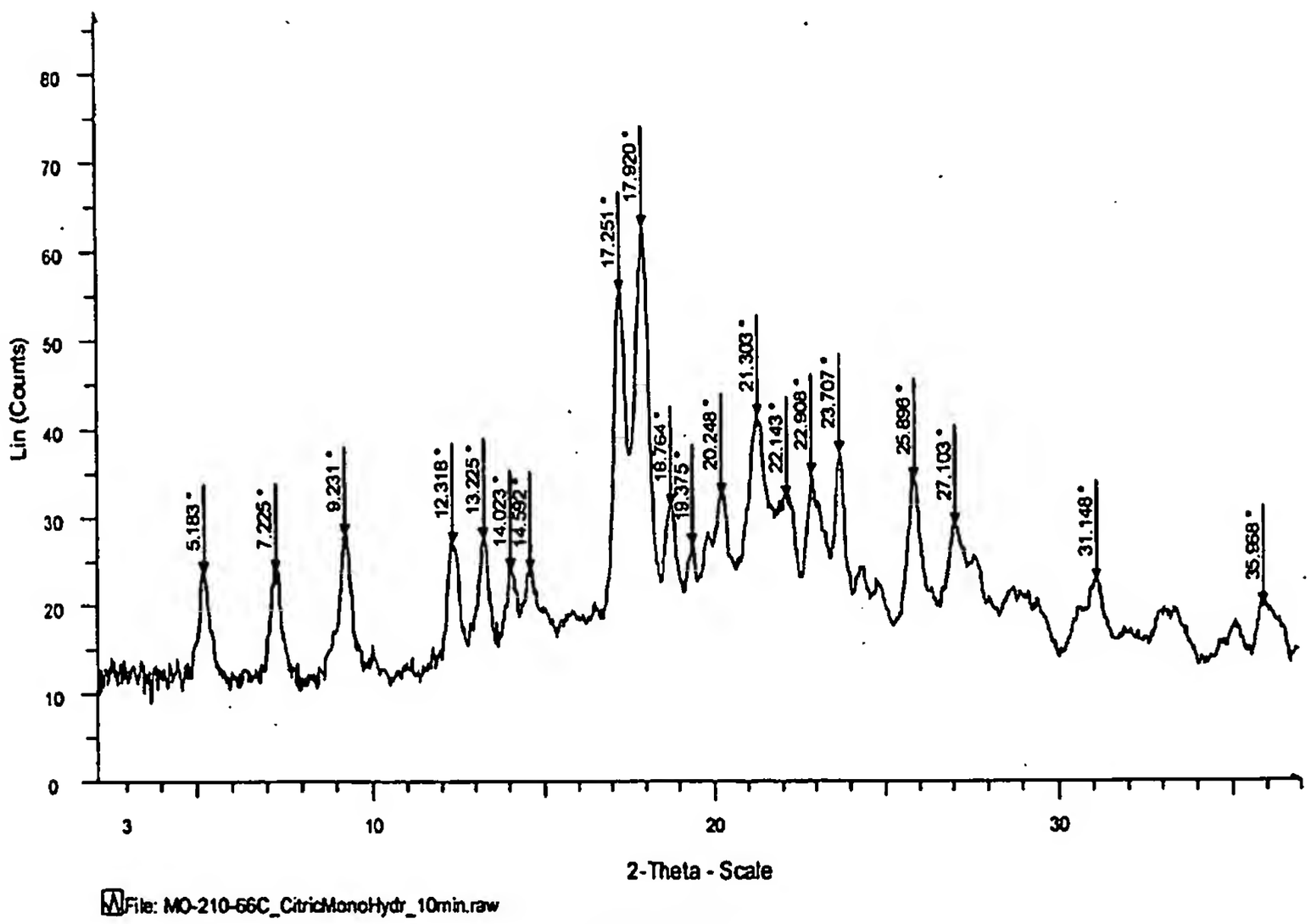


Figure 19

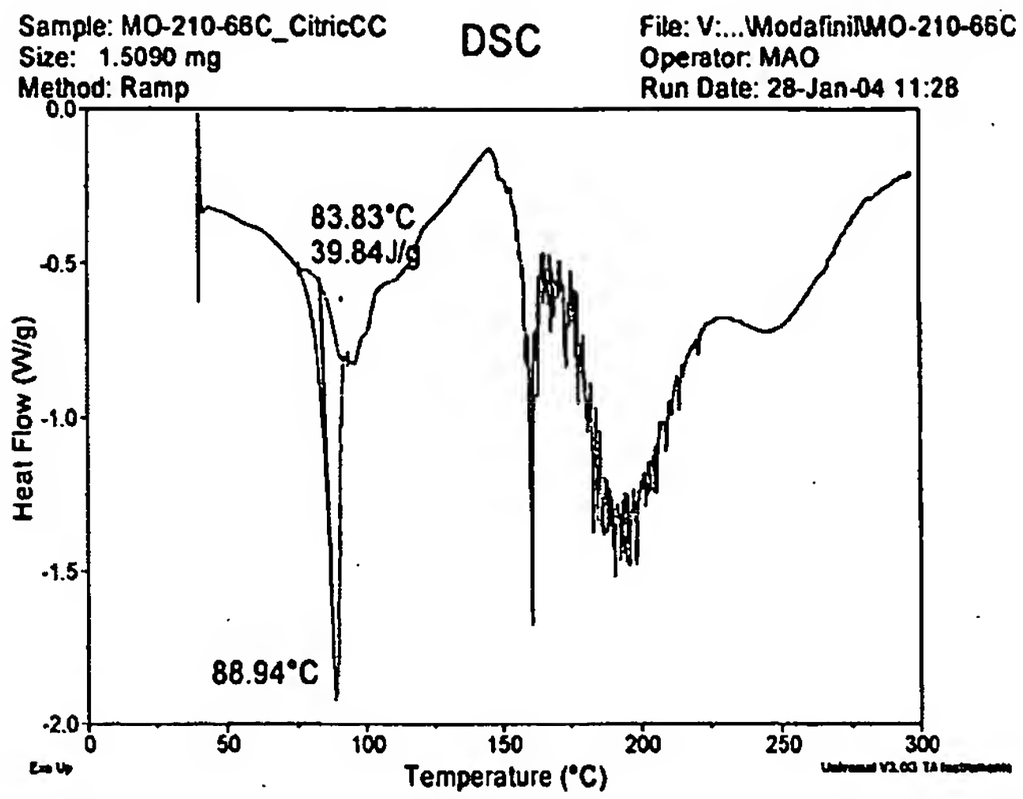
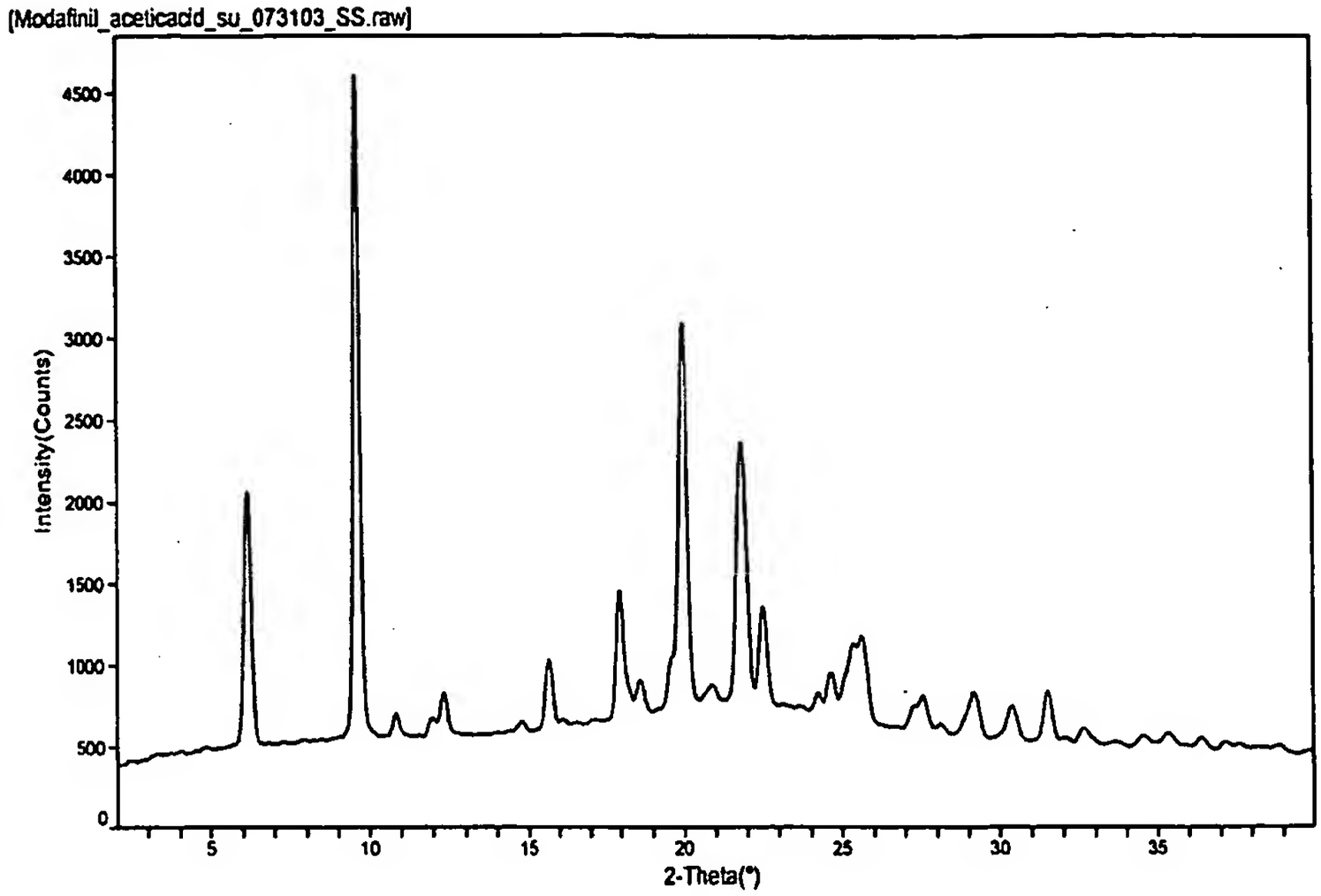

Sample: MO-210-66C_CitricCC
Size: 1.5090 mg
Method: Ramp
DSC
File: V:...\Modafinil\MO-210-66C
Operator: MAO
Run Date: 28-Jan-04 11:28
83.83°C
39.84J/g
88.94°C
Heat Flow (W/g)
0.0
-0.5
-1.0
-1.5
-2.0
0
50
100
150
200
250
300
Temperature (°C)

Figure 20



2-Theta Degrees
6.169
9.629
10.810
11.990
12.349
14.771
15.690
17.970
18.610
19.990
20.929
21.830
22.510
24.248
24.669
25.611
27.569
28.093
29.190
30.390

Figure 21

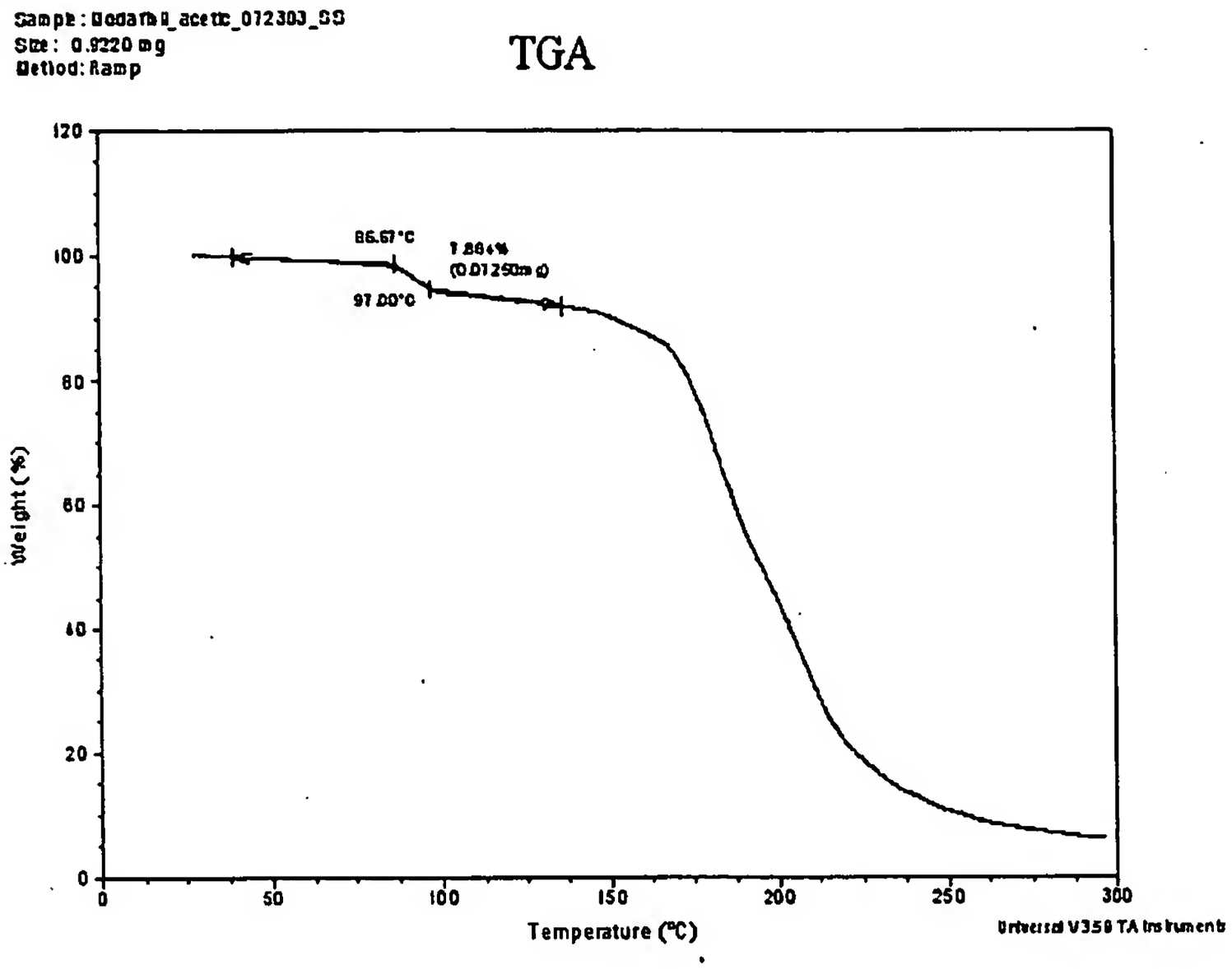

Sample: Sodium_acetic_072303_SS
Size: 0.9220 mg
Method: Ramp
TGA
86.67°C
1.884%
(0.01736mg)
97.00°C
120
100
80
60
40
20
0
Weight (%)
0
50
100
150
200
250
300
Temperature (°C)
Universal V3.9B TA Instruments

Figure 22

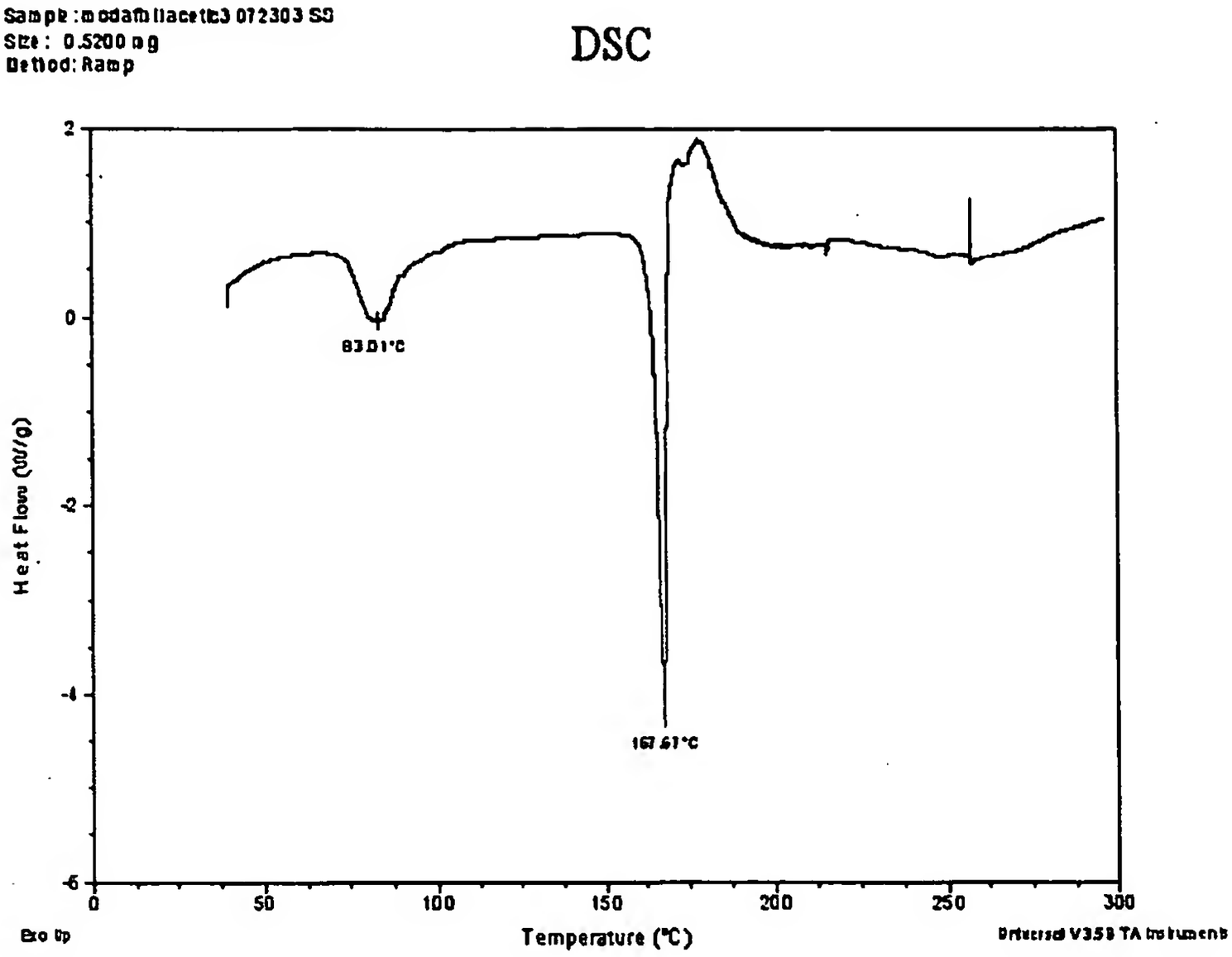
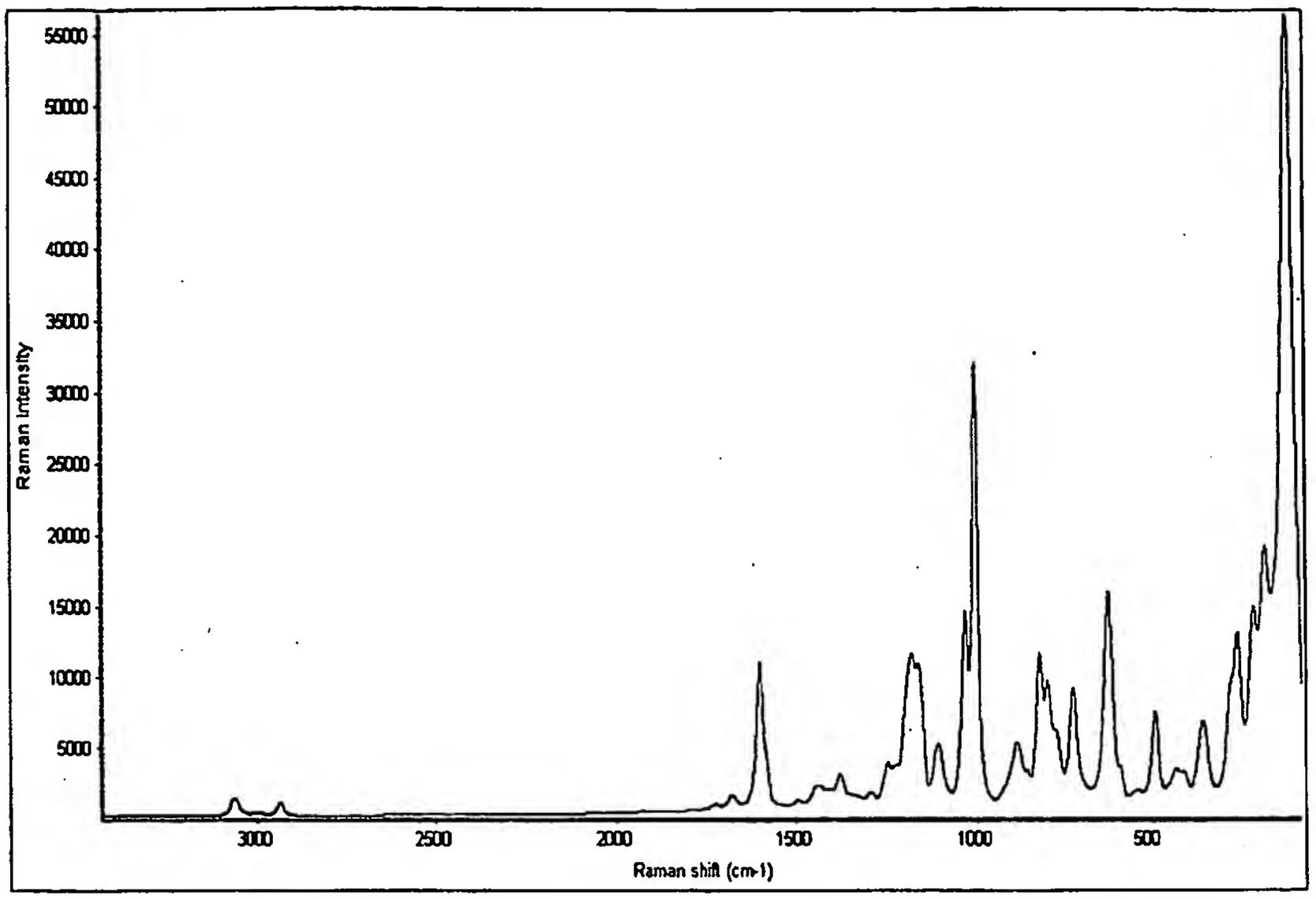

Sample :modafinilacetic3 072303 S3
Size : 0.5200 mg
Method: Ramp
DSC
2
0
-2
-4
-6
Heat Flow (W/g)
83.01°C
167.61°C
0
50
100
150
200
250
300
Exo Up
Temperature (°C)
Universal V3.5B TA Instruments

Figure 23



Position:	124.38	Intensity:	56488.199
Position:	1003.39	Intensity:	32065.602
Position:	190.78	Intensity:	19242.451
Position:	624.92	Intensity:	16043.604
Position:	1032.16	Intensity:	14613.689
Position:	267.46	Intensity:	13128.612
Position:	822.14	Intensity:	11636.112
Position:	1181.06	Intensity:	11607.680
Position:	1601.13	Intensity:	11005.503
Position:	725.91	Intensity:	9152.309
Position:	494.61	Intensity:	7458.328
Position:	362.59	Intensity:	6747.720
Position:	887.40	Intensity:	5256.710
Position:	1106.67	Intensity:	5119.203

Figure 24

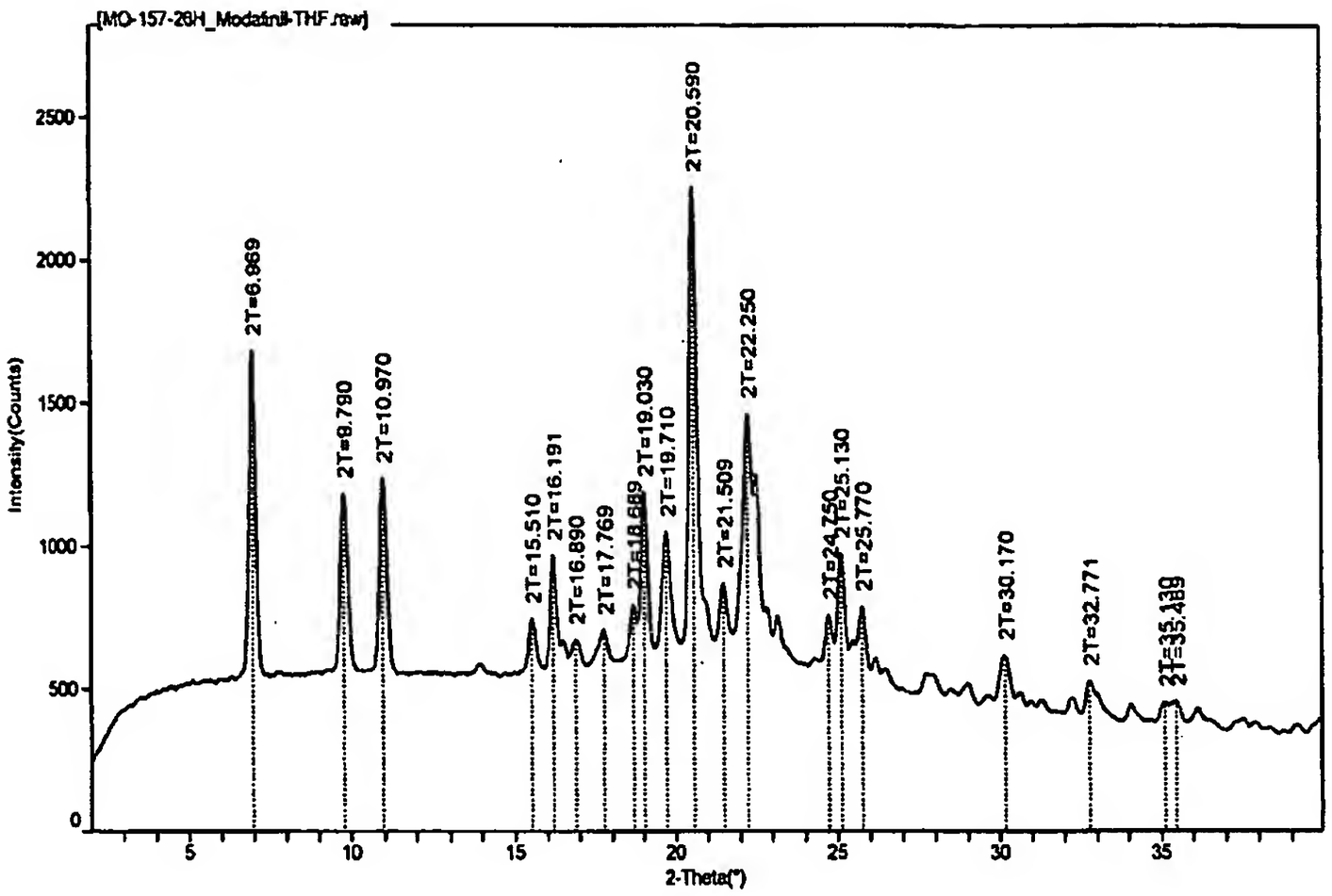


Figure 25

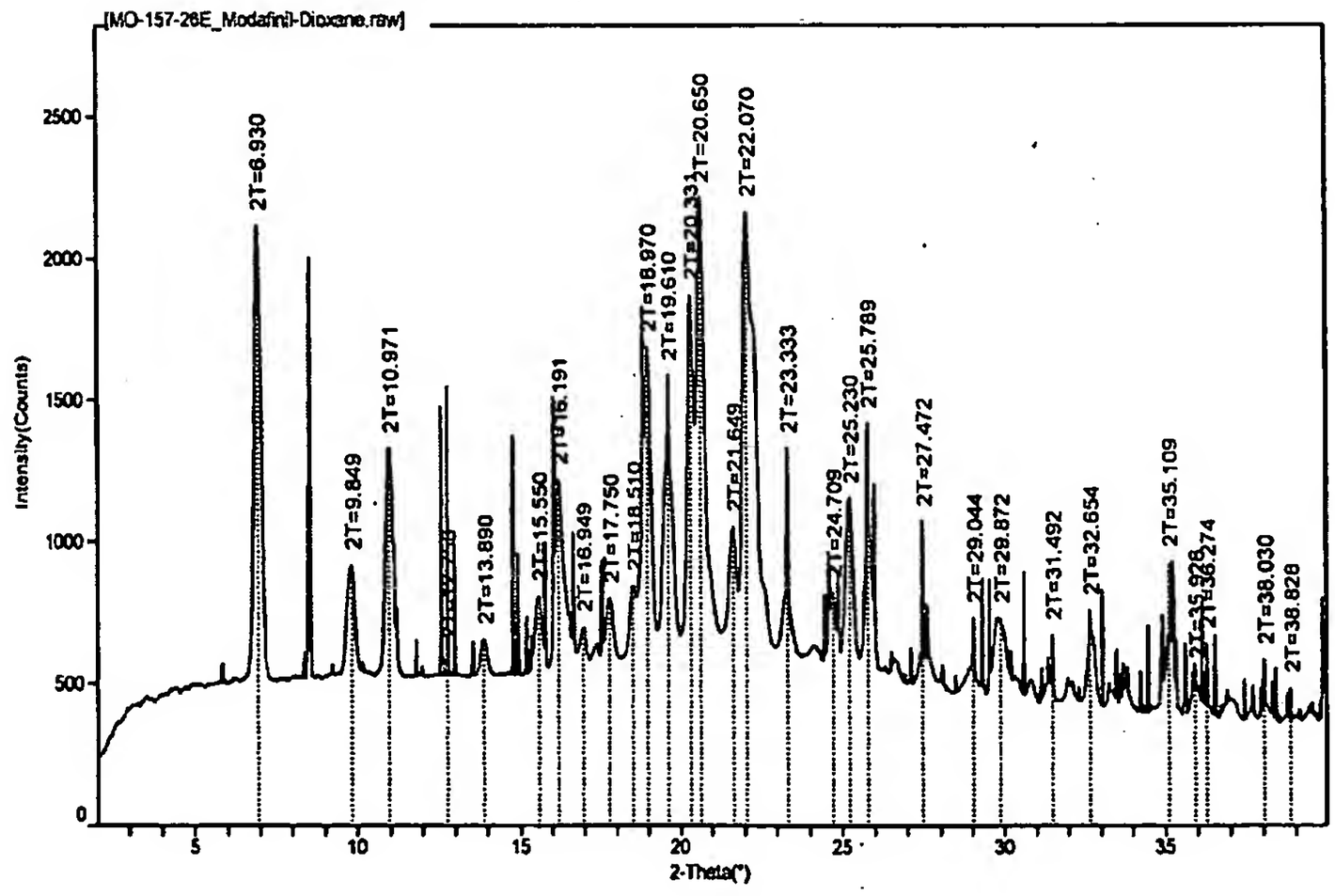


Figure 26

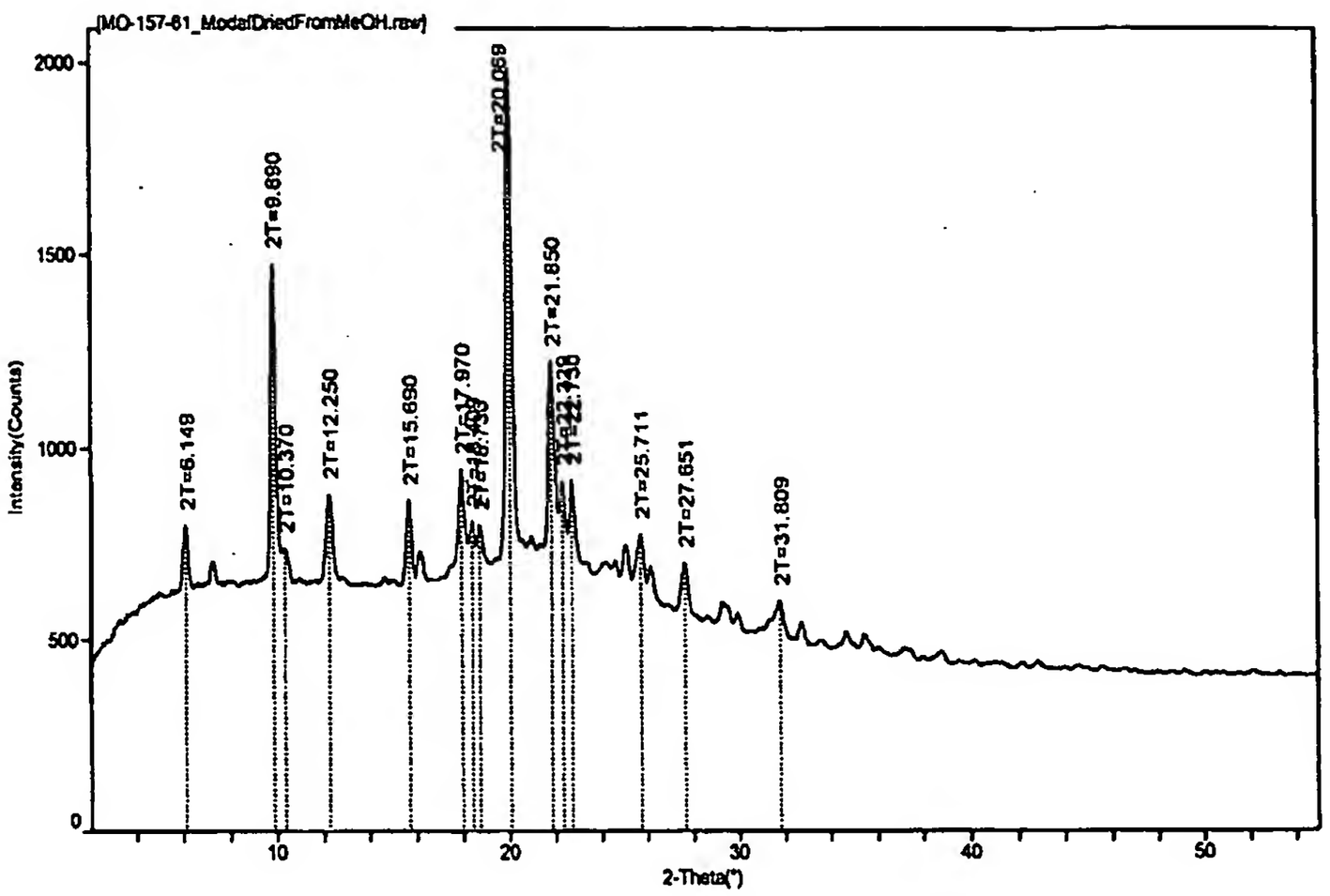


Figure 27

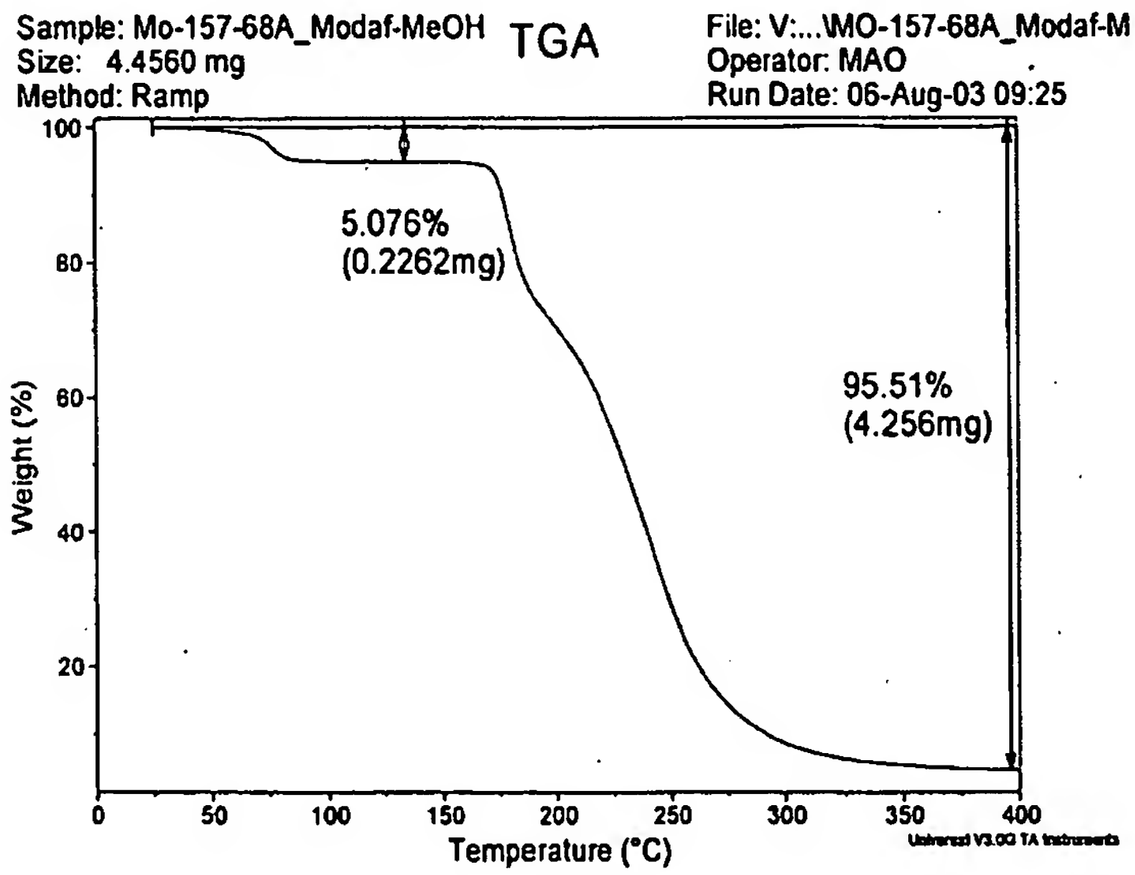


Figure 28

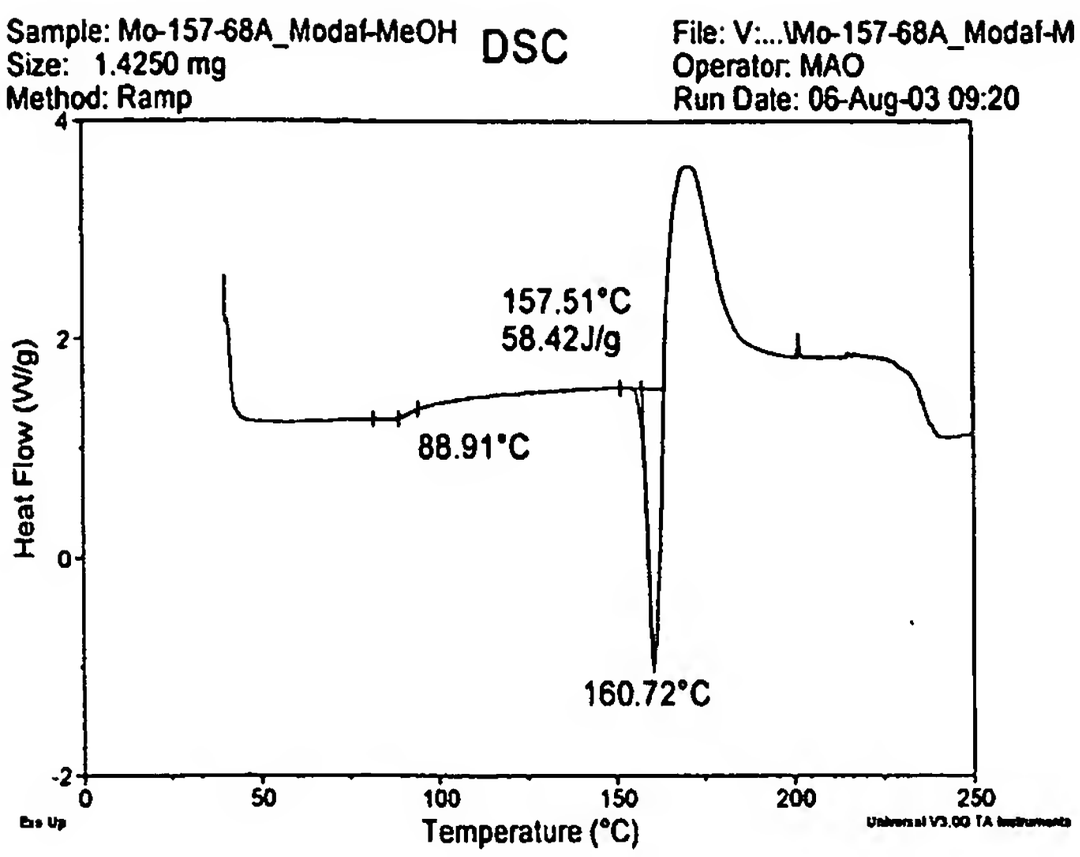


Figure 29

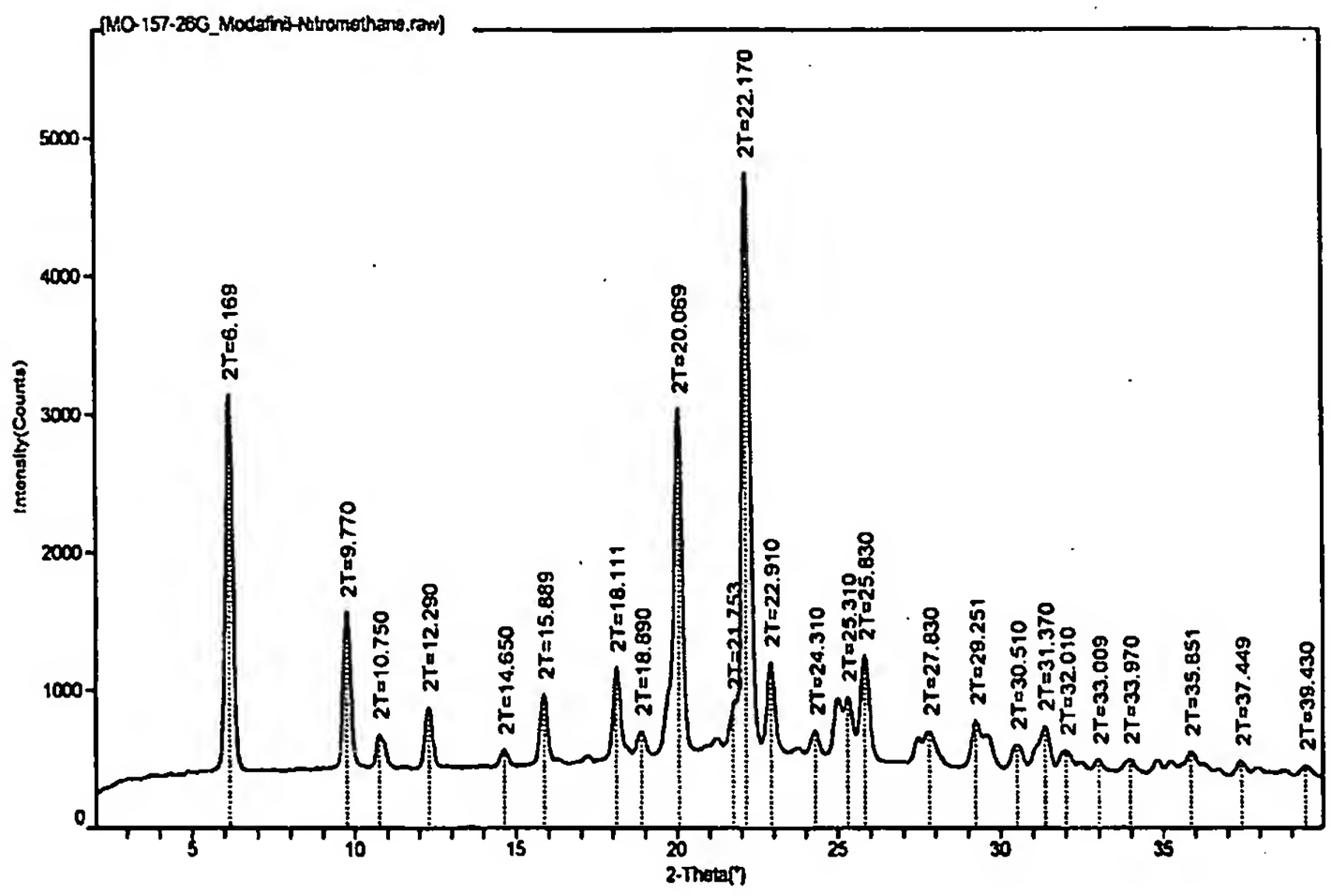


Figure 30

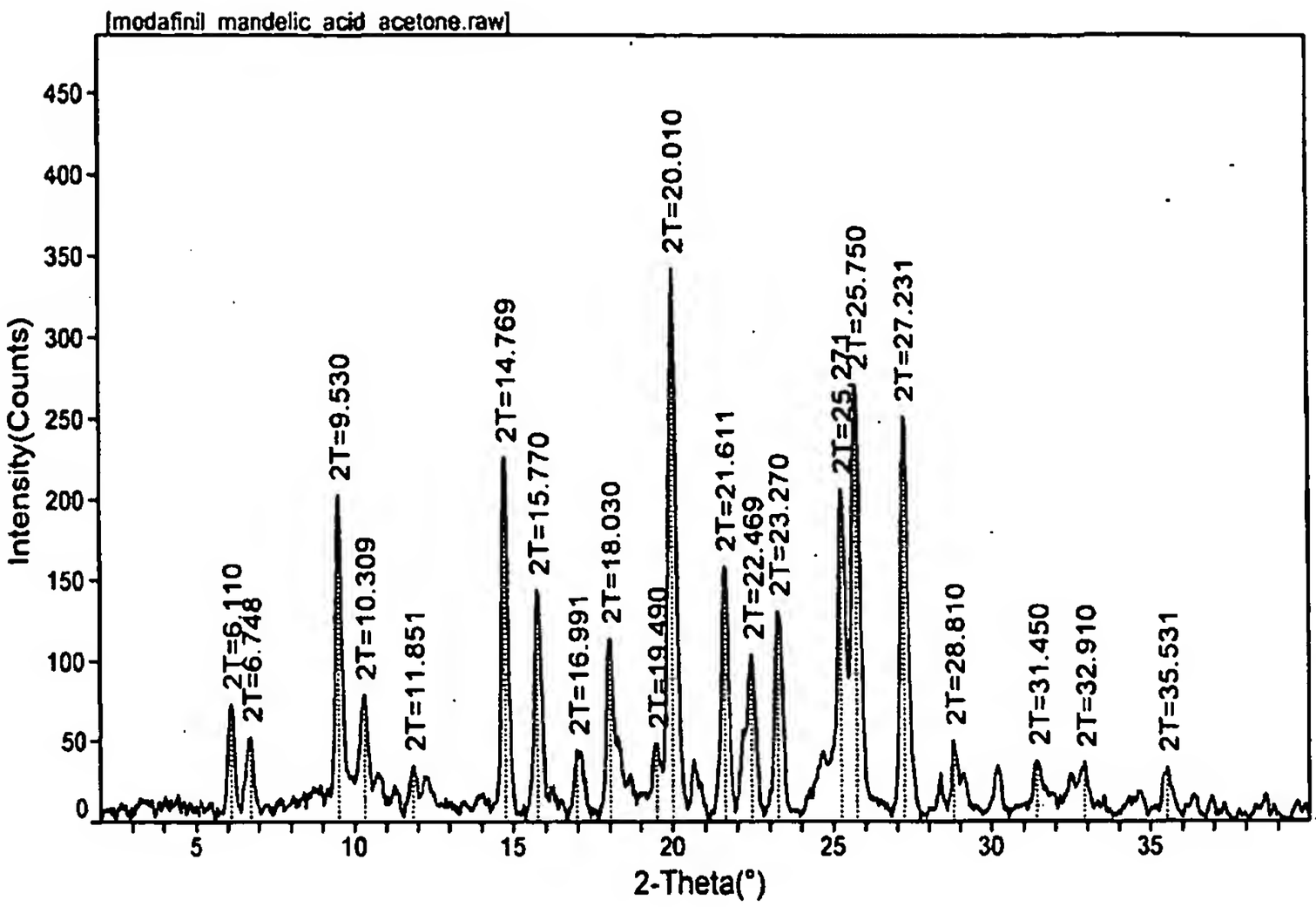

[modafinil mandelic acid acetone.raw]
Intensity(Counts)
2-Theta(°)
2T=6.110
2T=6.748
2T=9.530
2T=10.309
2T=11.851
2T=14.769
2T=15.770
2T=16.991
2T=18.030
2T=19.490
2T=20.010
2T=21.611
2T=22.469
2T=23.270
2T=25.271
2T=25.750
2T=27.231
2T=28.810
2T=31.450
2T=32.910
2T=35.531

Figure 31

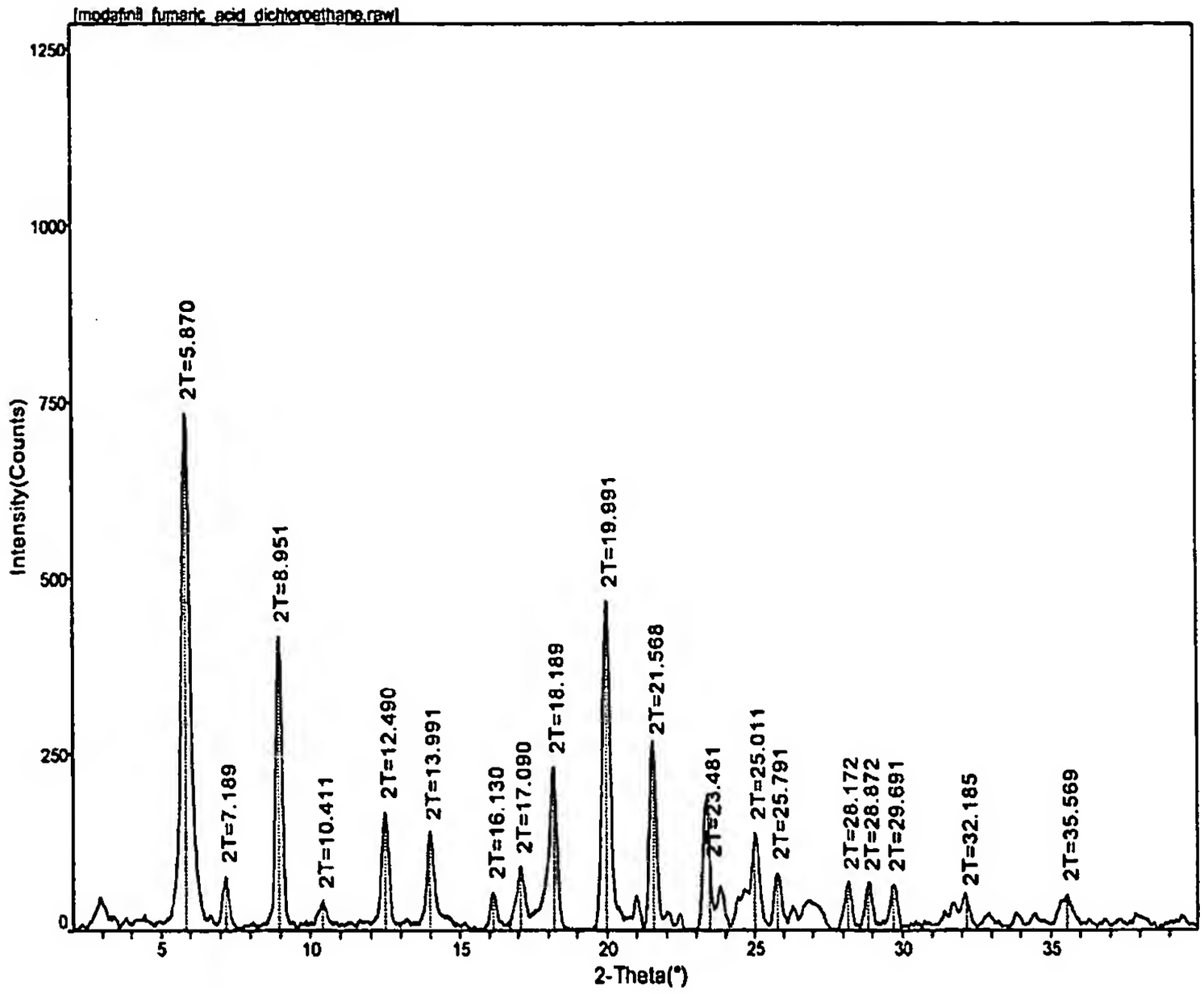


Figure 32

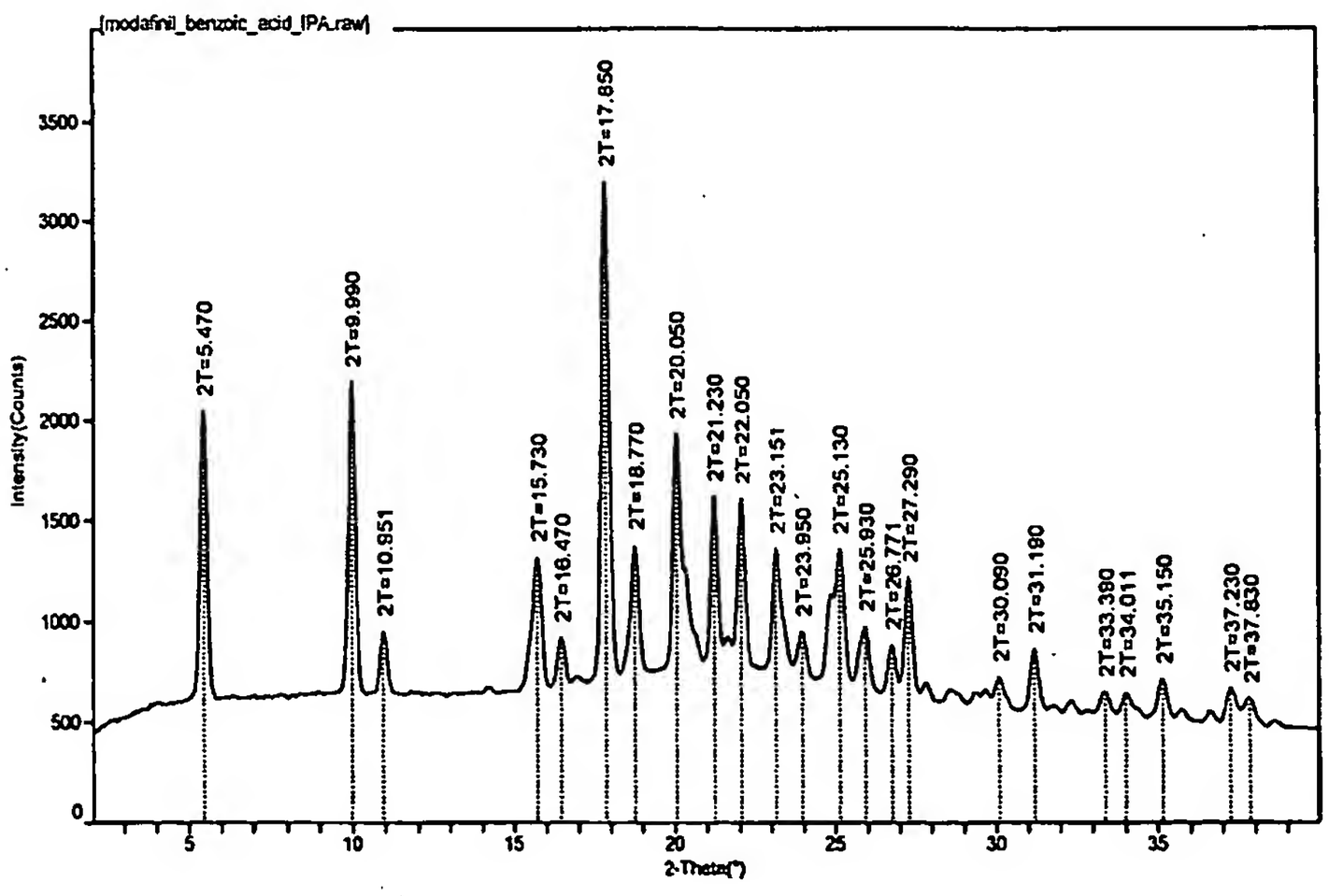


Figure 33

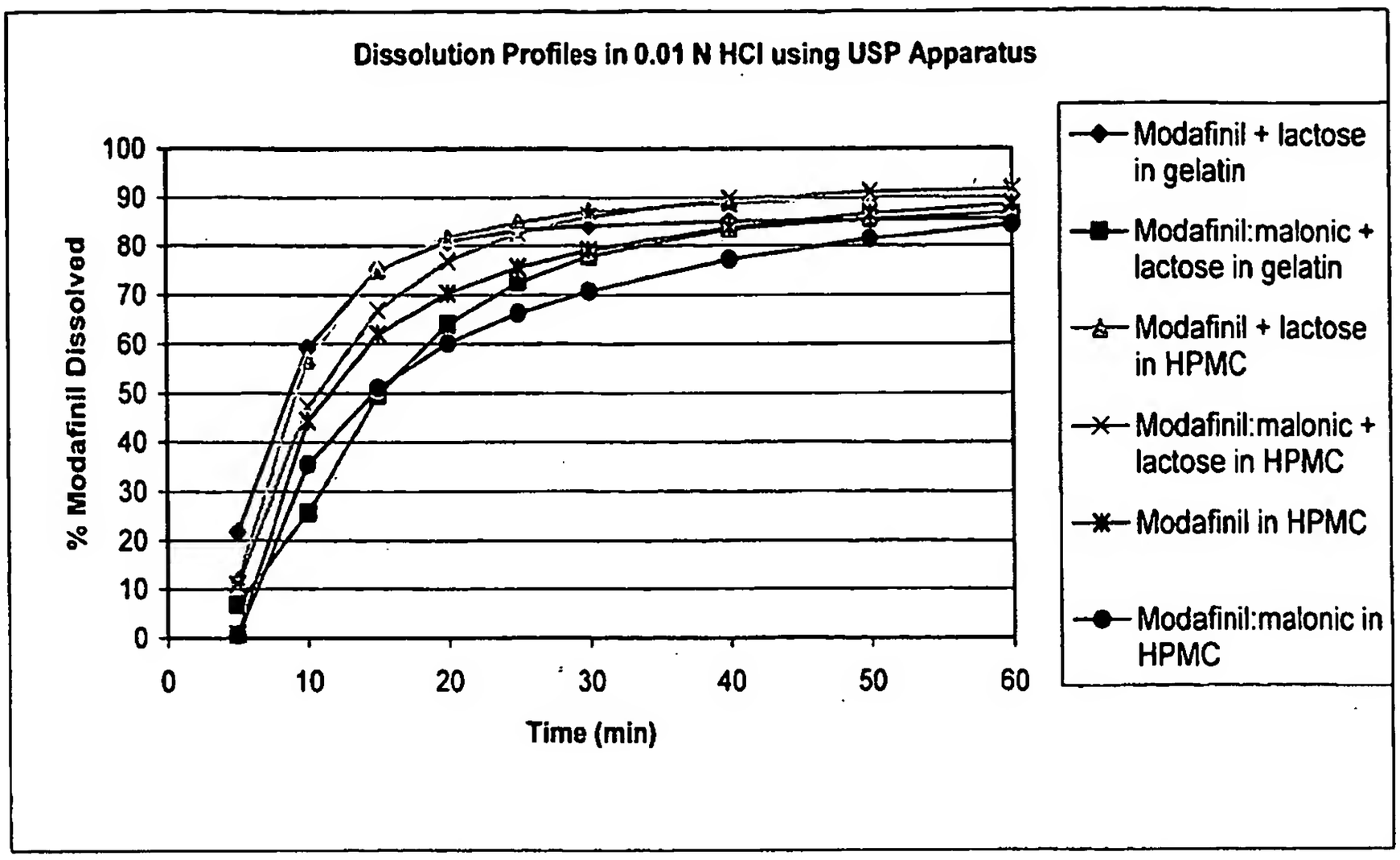


Figure 34

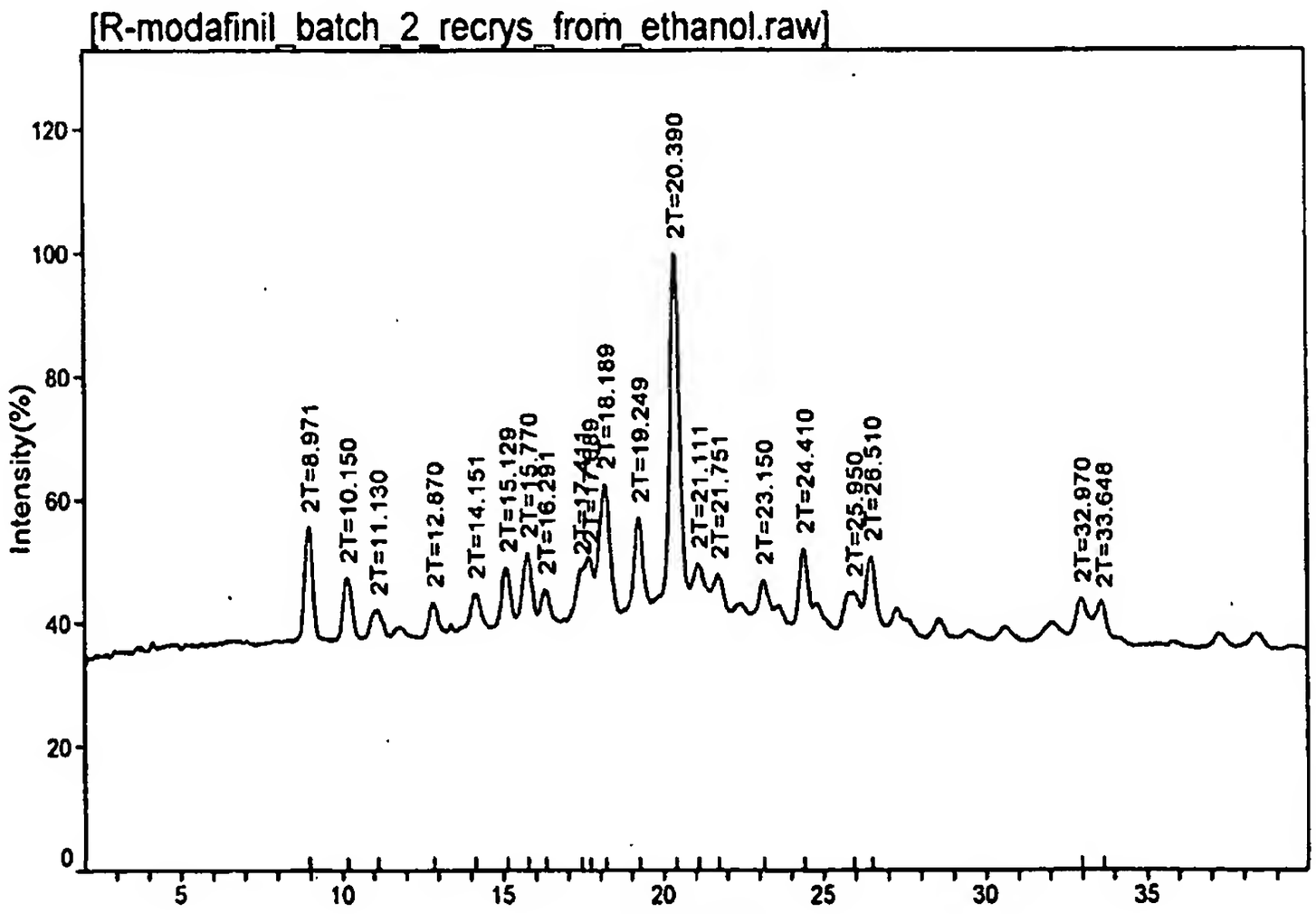


Figure 35

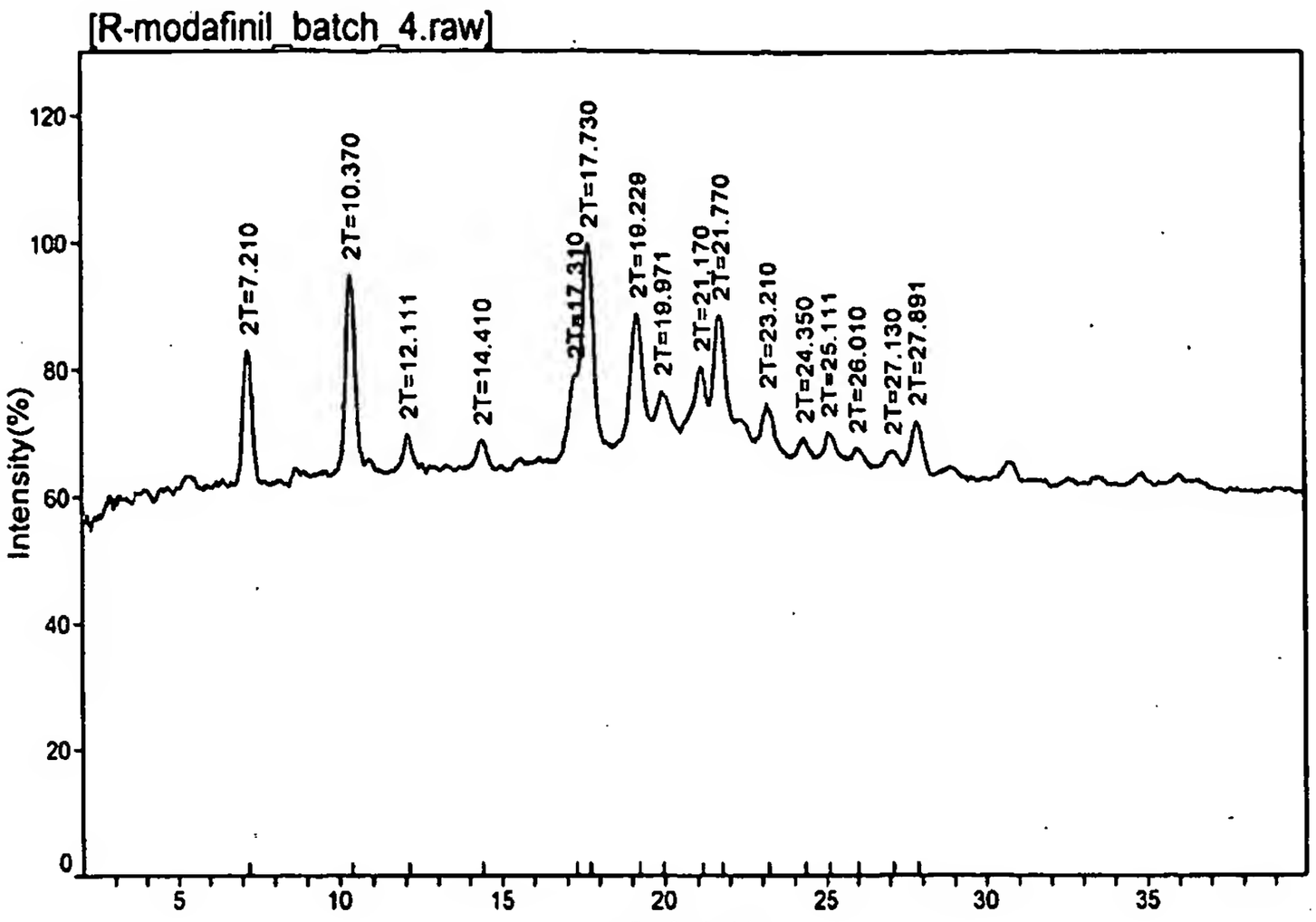


Figure 36

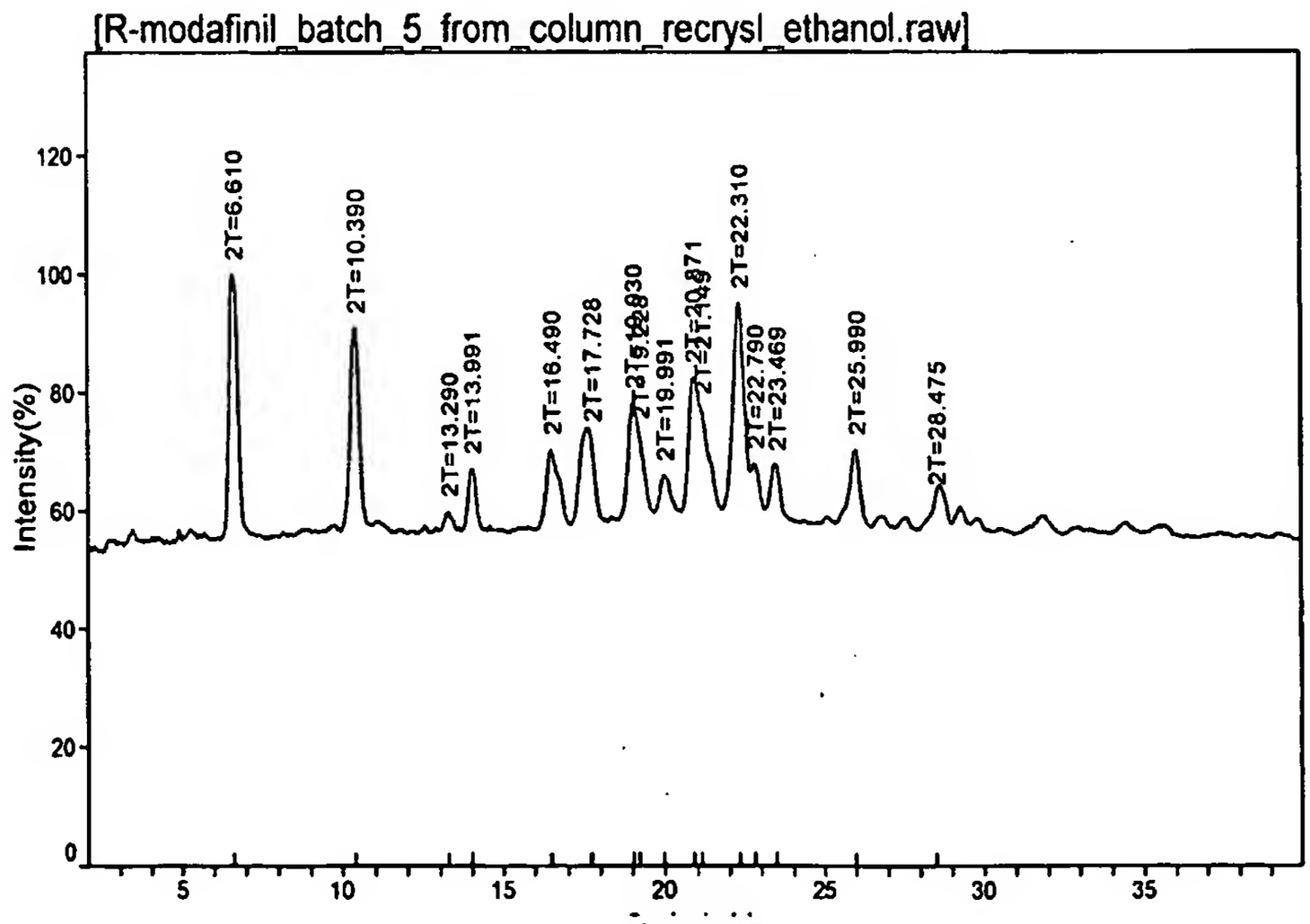


Figure 37

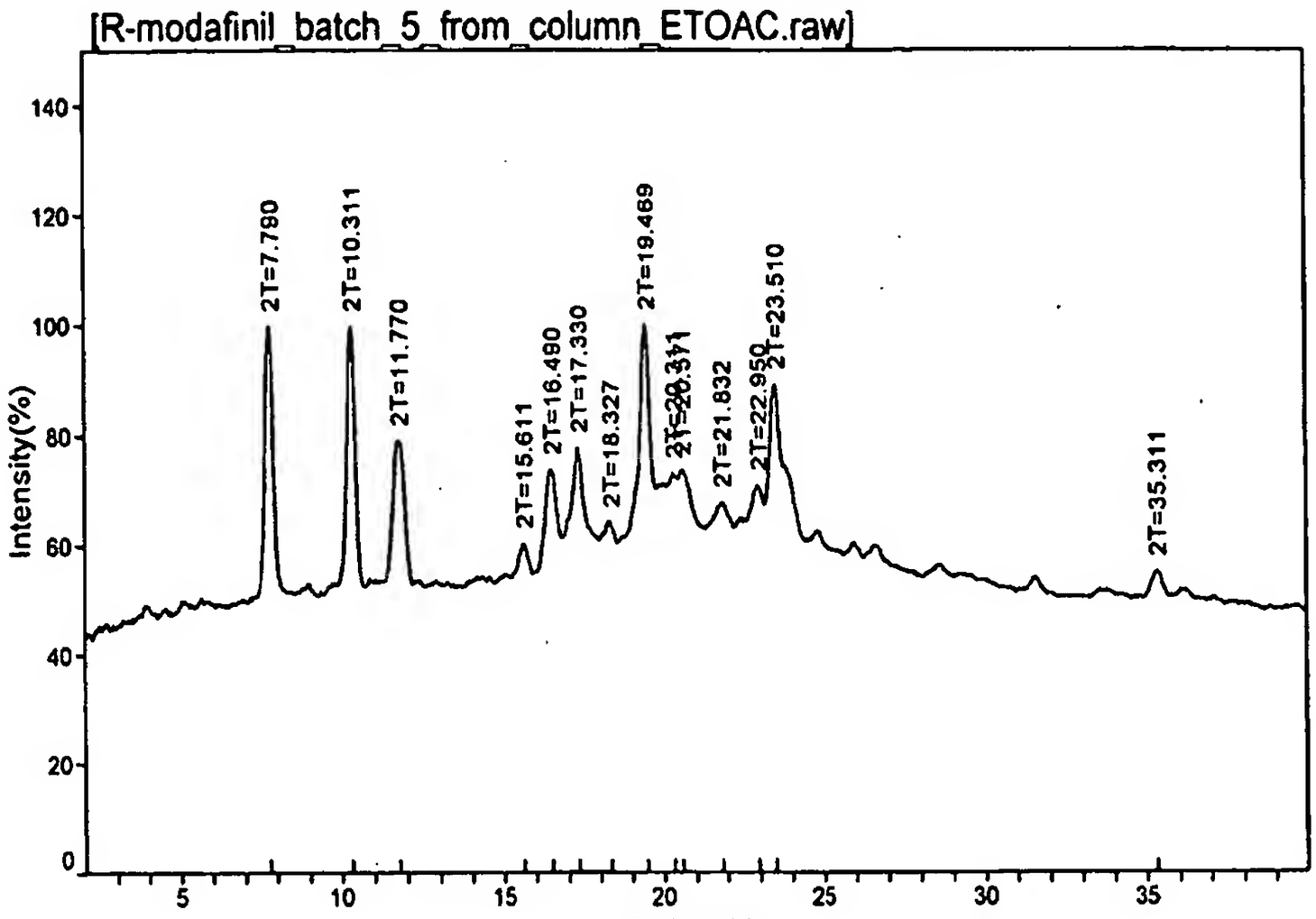

[R-modafinil_batch_5_from_column_ETOAC.raw]
Intensity(%)
140
120
100
80
60
40
20
0
5
10
15
20
25
30
35
2T=7.780
2T=10.311
2T=11.770
2T=15.611
2T=16.490
2T=17.330
2T=18.327
2T=19.469
2T=21.832
2T=23.510
2T=35.311

Figure 38